The Royal Australian and New Zealand College of Obstetricians and Gynaecologists

Excellence in Women's Health

Australian clinical practice guideline for the diagnosis and management of endometriosis

CONSULTATION DRAFT
Technical report

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Introduction

The National Action Plan for Endometriosis, launched in July 2018, provides priorities and actions for improving the awareness, understanding, treatment of, and research into, endometriosis and associated chronic pelvic pain in Australia. The Action Plan describes clinical management and care as one of its key priority areas. Currently, there are no national evidence-based clinical practice guidelines for the diagnosis and management of endometriosis for use in Australia.

In December 2018, the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) was contracted by the Commonwealth Department of Health to develop an Australian clinical practice guideline for the diagnosis and management of endometriosis (hereafter referred to as the **Australian Endometriosis Guideline**), with content drawn from one or more existing evidence-based guidelines on endometriosis.

During the early stages of the project, RANZCOG established an Organising Group to provide strategic, high-level input and advice relating to scope, approach and governance arrangements for the development of the Australian Endometriosis Guideline, and the expertise required on the Endometriosis Expert Working Group (EEWG). The role of the EEWG was to provide expertise and advice throughout the guideline development process.

Purpose of this document

The purpose of the technical report is to document the new evidence identified from the literature searches, and the Evidence-to-Decision framework for adopting, adapting, or developing new recommendations. A modified GRADE-ADOLOPMENT approach using GRADEpro software provided structure and transparency to decisions on whether new judgements of the evidence differed from the original assessment in the existing guidelines.

Methods

Identification and selection of relevant guidelines for adoption/ adaptation

At the commencement of development of this guideline, the Commonwealth Department of Health indicated a preference for using a recent, high-quality endometriosis guideline – the National Institute for Health and Care Excellence's (NICE) *Endometriosis: diagnosis and management (NG73)*, September 2017[1] – as a starting point for development of the Australian Endometriosis Guideline. The EEWG agreed with this approach in principle, but the final decision was informed by a Scoping Review to confirm that the NICE 2017 Guideline was the most suitable of the existing endometriosis guidelines for adoption/adaptation.

Identification of existing endometriosis guidelines

The methodologists relied on direction from the Chair of the EEWG to identify published guidelines that could be considered as the basis for an Australian guideline on the diagnosis and management of endometriosis. In addition to the **NICE 2017 Guideline**, the Chair nominated two guidelines that are also commonly referred to by Australian healthcare professionals: the European Society of Human Reproduction and Embryology (ESHRE) *Management of women with endometriosis*, September 2013[2] (hereafter referred to as the **ESHRE 2013 Guideline**), and the World Endometriosis Society (WES) *Consensus on current management of endometriosis*, 2013[3] (hereafter referred to as the **WES 2013 Consensus**).

Development methods and scope of existing endometriosis guidelines

Table 1 provides a summary of the existing guidelines on endometriosis, including the methods used to develop each guideline.

Table 1 Summary of methods to develop existing guidelines on endometriosis

	NICE 2017 Guideline	ESHRE 2013 Guideline	WES 2013 Consensus[4]
Title	NICE Guideline (NG73): Endometriosis: diagnosis and management	ESHRE Guideline: Management of women with endometriosis	Consensus on current management of endometriosis
Publication year	September 2017	September 2013	March 2013
Country	UK	Europe[5]	Global[6]
Method used to identify evidence base (search date)	Systematic literature searches (updated Dec 2016)	Systematic review (Jan 2012)	"Extensive literature search" (Jul – Aug 2011)
Considerations when assessing the evidence base	Risk of bias Inconsistency Indirectness Imprecision Publication bias Clinical significance Cost-effectiveness Evidence gaps	Level of evidence Quality of evidence Validity Applicability	Mechanism of action Volume of evidence Consistency of evidence Applicability of evidence Effectiveness Adverse effects GRADE – evidence quality Evidence gaps

[1] Available at https://www.nice.org.uk/guidance/ng73 ; accessed 28 May 2019
[2] Available at https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Endometriosis-guideline ; accessed 28 May 2019
[3] Available at https://academic.oup.com/humrep/article/28/6/1552/603470 ; accessed 28 May 2019
[4] Consensus process supported by literature reviews (WES 2013 Supplementary data, Information 1).
[5] Guideline Development Group members were from the Netherlands, UK, Portugal, Belgium, Finland, Germany and Israel.
[6] Invited 51 national and international societies to participate in the WES Consensus. In total, 56 representatives from 34 organisations

	NICE 2017 Guideline	ESHRE 2013 Guideline	WES 2013 Consensus[4]
Method used to assess the evidence base	GRADE	ESHRE quality assessment; evidence table using GIN format	GRADE (EtD process is not transparently reported)
Method used to link evidence to recommendations	GRADE	ESHRE grading, based on SIGN 2010	Consensus
Number of recommendations/GPPs	53 recommendations	52 recommendations; 32 GPPs[7]	59 consensus statements; 10 GPPs
Guideline quality using AGREE II	**Very good**	**Good**	**Fair**

Abbreviations: CPG, clinical practice guideline; ESHRE, European Society of Human Reproduction and Embryology; EtD, evidence-to-decision; GPP, Good Practice Point; NICE, National Institute of Health Care Excellence; SIGN, Scottish Intercollegiate Guidelines Network; SR, systematic review; WES, World Endometriosis Society.

a The three existing endometriosis guidelines were assessed using the Appraisal of Guidelines for Research & Evaluation II (AGREE II) tool (https://www.agreetrust.org/agree-ii/) and were classified as very good, good, fair or poor in quality.

The **NICE 2017 Guideline** contains the most recent evidence and used the most rigorous and transparent development process following the GRADE approach. The **ESHRE 2013 Guideline** was developed using ESHRE methods, which did not follow GRADE. The **WES 2013 Consensus** followed GRADE evidence appraisal methods, but the evidence-to-decision process is not transparently reported.

Selection of an existing endometriosis guideline for adoption/adaptation

When assessing the suitability of the existing guidelines for adoption/adaptation, the EEWG considered six domains:[8]

1. Relevance
2. Currency
3. Trustworthiness
4. Access to evidence
5. Implementability
6. Acceptability.

The **NICE 2017 Guideline** was considered the clear frontrunner for adoption/adaptation for the following reasons:

- it rated higher using the AGREE II instrument than the other two guidelines
- it is methodologically sound and followed a transparent development process using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology
- it is well-documented (GRADE Evidence Profile Tables, Evidence Summary Tables, Evidence Statements and Evidence-to-Decision summaries are available)
- the evidence review was updated more recently than the other guidelines, in December 2016.

Appendix A contains a summary of the research questions, evidence statements and recommendations in the **NICE 2017 Guideline**.

[7] The ESHRE 2013 Guideline contains 85 recommendations/GPPs because one GPP relating to ART for infertility is duplicated in different sections. The ESHRE 2014 publication states that there are 51 recommendations and 32 GPPs (83 in total). The discrepancy is due to one recommendation on biomarkers being combined into a single recommendation in the publication.

[8] Taken from NHMRC Guidelines for Guidelines: Adopt, adapt or start from scratch; available at https://www.nhmrc.gov.au/guidelinesforguidelines/plan/adopt-adapt-or-start-scratch; last updated 22/11/2018.

Overview of approach to develop an Australian endometriosis guideline

At the first meeting of the EEWG on 18 July 2019, members agreed that the Australian Endometriosis Guideline should be broader in scope than the NICE 2017 Guideline. The topics for inclusion were further refined in teleconferences with a PICO Working Group on 08 August 2019 and 02 October 2019, and later agreed by the full EEWG who approved the Research Protocol. Table 2 shows the additional topics, as specified in the Research Protocol, which are not covered in the NICE Guideline. As a consequence of the broader scope, a partial adaptation or hybrid approach was used to develop the Australian Guideline, whereby some recommendations were adopted or adapted from NICE (with or without contextualisation) and some were developed from scratch, based on new evidence reviews.

Appendix A contains a complete list of research questions and recommendations from the NICE 2017 Guideline.

Table 2 Agreed scope for the Australian Endometriosis Guideline indicating expansion in scope from the NICE 2017 Guideline

Scope for the Australian Endometriosis Guideline	Included in the NICE 2017 Guideline?
Who the guideline is for	
Healthcare professionals working with people with endometriosis	YES
People with endometriosis	YES
Families and carers of people with endometriosis	YES
The public	YES
Who is the focus	
People with confirmed or suspected endometriosis	YES
People with asymptomatic endometriosis discovered incidentally	YES
Young people (aged 17 and under) with endometriosis	YES
Infertile people with endometriosis	YES
People with endometriosis occurring outside the pelvis	NO
People with persistent pelvic pain who are suspected to have endometriosis	NO
Postmenopausal people with endometriosis	NO
Pregnant people with endometriosis	NO
Aboriginal and Torres Strait Islander people with endometriosis	NO
Non-binary people with endometriosis	NO
Key areas covered[9]	
Secondary prevention of endometriosis	NO[10]
Signs and symptoms of endometriosis	YES
Information and support	YES
Risk of cancer of the reproductive organs	YES[11]
Timing: duration of symptoms before laparoscopy	YES
Organisation of care	YES
Primary care	NO
Specialist services	YES
Endometriosis care in rural and remote settings	NO
Effectiveness of validated tools for assessment of the severity of endometriosis	NO
Referral for people with suspected or confirmed endometriosis	YES
Diagnosis of endometriosis	YES

[9] The EEWG originally suggested the effectiveness of tools for the assessment of disease severity as a topic for inclusion in the Australian Guideline but the PICO Working Group agreed not to include this topic as tools are being developed as part of the National Action Plan.
[10] The PICO Working Group agreed that primary prevention should not be reviewed for the Australian Guideline.
[11] The PICO Working Group agreed that risk of cancer should be mentioned but not systematically reviewed for the Australian Guideline.

Scope for the Australian Endometriosis Guideline	Included in the NICE 2017 Guideline?
Clinical examination	NO
Ultrasound/sonography	YES
Biomarkers	YES
Computed tomography (CT)	NO
Magnetic resonance imaging (MRI)	YES
Laparoscopy/surgical diagnosis	YES
Diagnosis of adenomyosis	NO
Staging systems	YES
Pharmacological management	YES
Analgesics	YES
Medicinal cannabis	NO
Neuromodulators	YES
Hormonal medical treatments	YES
Alternatives to pharmacological and surgical management	YES
Surgical management (including endometrioma surgery)	YES
Management strategies if fertility is a priority	YES
Investigation of fertility problems associated with endometriosis treatments	NO[12]
Management of menopausal symptoms associated with surgical treatment	NO[13]
Management specific to adenomyosis	NO
Follow-up for people with asymptomatic endometriosis	NO

Figure 1 provides an overview of the approach that was used to develop recommendations for the Australian Endometriosis Guideline, using the NICE 2017 Guideline as the source guideline for adoption/adaptation. The starting point for the flow diagram is consideration of priority topics that should be covered in the Australian Guideline (**Steps 1, 2 and 3** in Figure 3-1), which occurred at the first meeting of the EEWG. **Step 4** in the flow chart is addressed by Table 2, which indicates whether the topics are included in the NICE Guideline. The PICO Working Group subsequently worked through **Steps 5, 6, 7, 8 and 9** in the flow diagram (in collaboration with the methodologists), to refine the NICE research questions and the NICE evidence selection criteria, and to develop entirely new questions and evidence selection criteria (presented in **Appendix B** of this technical report).

The approach in Figure 1 allows for systematic evidence update of research questions that are based on the NICE questions (**Steps 10, 11 and 12**), and *de novo* systematic review for new research questions or new components of research questions, such as new populations or interventions (**Step 22**). As shown in **Steps 12 and 22**, GRADE methodology was used, where appropriate, to appraise the entire body of evidence. In the latter stages of the process, EEWG subgroups met to consider the synthesised evidence and develop recommendations using an Evidence-to-Decision framework (**Steps 13 through 21** and **Steps 23 through 26**).

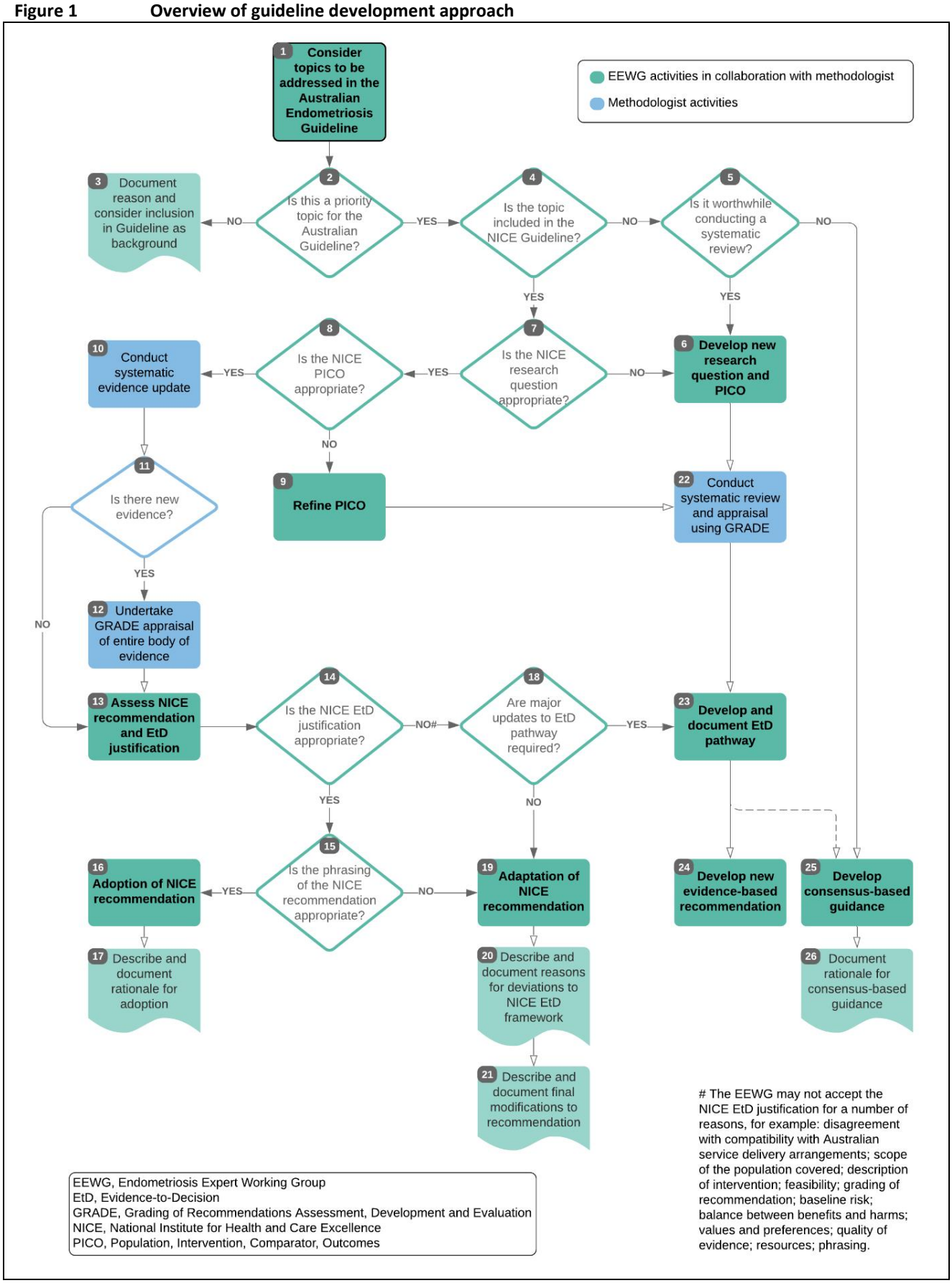
Evidence-based recommendations were constructed using four possible approaches:

1. adopt recommendations from the NICE 2017 Guideline without modification,
2. adapt recommendations from the NICE 2017 Guideline to the Australian context,
3. develop new recommendations based on the evidence from the NICE 2017 Guideline, and
4. develop new recommendations based on entirely new evidence synthesis.

[12] The PICO Working Group subsequently agreed that this topic should not be systematically reviewed in the Australian Guideline, but a Committee Opinion could be developed providing advice on when to refer people to a fertility specialist.

[13] The PICO Working Group subsequently agreed that this topic should not be systematically reviewed in the Australian Guideline as there is other guidance relating to management of menopausal symptoms that could be generalised to people after surgery for endometriosis.

Figure 1 Overview of guideline development approach



Research questions

Table 3 presents the final list of research questions for the Australian Endometriosis Guideline, which were developed through collaboration with the EEWG at a meeting on 18 July 2019 and teleconferences with a PICO Working Group on 08 August 2019 and 02 October 2019. The research questions are largely based on the questions underpinning the NICE 2017 Guideline, with refinement of the wording by the PICO Working Group and methodologists.

There are **20** agreed research questions for the Australian Endometriosis Guideline, five of which are entirely new questions that were not posed in the NICE 2017 Guideline. Some research questions have been grouped together as they address the same topic (e.g. pharmacological management encompasses analgesics [Q7a], neuromodulators [Q7b] and hormonal medical treatments [Q7c]).

The research questions have been placed in a sequence that *approximates* the patient journey, starting with presentation (signs and symptoms), provision of information and support, organisation of care, referral, diagnosis, staging, treatment, then follow-up and secondary prevention. This sequence was driven to some extent by the evidence review process, whereby all questions within a 'topic' (e.g. diagnosis, treatment, etc.) were reviewed together.

Of the 20 questions in Table 3, the PICO Working Group agreed not to undertake systematic reviews for four questions. The rationale is provided below.

<u>Organisation of care</u>

Q4a. In people with endometriosis, do specialist endometriosis services improve patient outcomes?

This is a broader policy question and is particularly relevant for the UK setting where specialist endometriosis services are already established. The question was systematically reviewed for the NICE 2017 Guideline and no relevant clinical or economic evidence was identified. The EEWG agreed that any new published evidence will be setting and context specific, and is unlikely to be applicable to the Australian setting. As such, this question was not prioritised for update in the Australian Guideline.

Q4b. When should people with endometriosis be referred from primary care to gynaecological specialist services?

Although this is an important 'new' question that should be addressed in the Australian Guideline, the topic was not considered suitable for systematic review.

Q4c. When should gynaecologists seek interdisciplinary input to manage people with endometriosis?

Although this is an important 'new' question that should be addressed in the Australian Guideline, the topic was not considered suitable for systematic review.

<u>Risk of cancer of the reproductive organs</u>

Q2b. Do people with endometriosis have an increased risk of cancer of the reproductive organs?

This question was systematically reviewed for the NICE 2017 Guideline. The Guideline Development Committee noted that many people with endometriosis ask questions about whether or not the condition is associated with an increased risk of cancer. Even though very large population-based studies were identified, the Committee were cautious about drawing conclusions from the results because the evidence base was generally of low to very low quality and an absolute risk could not be derived from these data. The Committee concluded that no recommendations should be made based on the available evidence because the potential harms associated with misinterpretation or over-interpretation of any recommendation based on this data would outweigh any benefits conferred by people being specifically informed about this data.

As a systematic update of the evidence base for this question was expected to consume considerable resources but not identify any new high quality evidence, it was agreed that a systematic review of this topic would not be undertaken for the Australian Guideline.

Prevention of endometriosis

Q12. What is the evidence for secondary prevention of endometriosis?

Secondary prevention of the recurrence of endometriosis and endometriosis-associated pain is clinically important in view of the recurrence rates reported after endometriosis surgery. The primary focus for secondary prevention of endometriosis is on postoperative hormonal therapies. The ESHRE 2013 Guideline notes that postoperative adjunctive hormonal therapies for endometriosis can be prescribed in two situations:

(i) for secondary prevention, which is defined as prevention of the recurrence of pain symptoms or the recurrence of disease in the long-term (more than 6 months after surgery); and

(ii) short-term treatment (within 6 months after surgery) with the aim of improving the outcome of surgery for pain.

Although the NICE 2017 Guideline did not explicitly distinguish these two situations when considering evidence relating to the effectiveness of hormonal treatment before or after surgery for treatment of endometriosis, they did assess longer term recurrence of endometriosis and reoperation rates. Therefore, Q9b in Table 3 (which is adapted from the NICE 2017 Guideline) already addresses secondary prevention of endometriosis using hormonal medical treatments. 'Recurrence' is also an outcome in other research questions relating to management: Q7b (neuromodulators), Q7c (hormonal medical treatments), Q8 (alternatives to pharmacological and surgical management), Q9a (surgical management) and Q9c (hysterectomy). Furthermore, recurrence is an outcome for Q11, which addresses follow up (including prophylactic surgery) in people who have received treatment and are asymptomatic. As such, evidence relevant to secondary prevention of endometriosis was expected to 'fall out' from other questions and a separate literature search specifically for secondary prevention was not warranted.

Of note, the NICE 2017 Guideline did not address primary prevention of endometriosis. However, a broad literature search on primary prevention was performed for the ESHRE 2013 Guideline to identify factors associated with the occurrence, prevalence and development of endometriosis. The relevant recommendations in the ESHRE Guideline state that the usefulness of oral contraceptives or physical exercise for the primary prevention of endometriosis is uncertain. The PICO Working Group agreed that there is unlikely to be new evidence that would result in an actionable recommendation.

Table 3 Summary of research questions for the Australian Endometriosis Guideline

#	Question	Topic	Research question	Question type	Question derivation	PICO table
1	Q1	Signs and symptoms	What are the signs and symptoms of endometriosis?	Prognostic	NICE Guideline (modified)	Table App 12
2	Q2a	Information and support	What information and support do people with endometriosis and their families find helpful?	Intervention	NICE Guideline (modified)	Table App 13
3	Q2b	Information and support – Risk of cancer	Do people with endometriosis have an increased risk of cancer of the reproductive organs?	Not for SR	NICE Guideline (modified)	NA
4	Q3	Timing of diagnosis and intervention	In people with suspected endometriosis, is early diagnosis and intervention beneficial?	Prognostic	NICE Guideline (modified)	Table App 14
5	Q4a	Organisation of care	In people with endometriosis, do specialist endometriosis services improve patient outcomes?	Not for SR	NICE Guideline	NA
6	Q4b	Referral to secondary care	When should people with endometriosis be referred from primary care to gynaecological specialist services?	Not for SR	New	NA
7	Q4c	Interdisciplinary care	When should gynaecologists seek interdisciplinary input to manage people with endometriosis?	Not for SR	New	NA
8	Q5a	Diagnosis – Endometriosis	What is the diagnostic performance of clinical examination, ultrasound, CT scan, MRI, biomarkers, and surgery in diagnosing endometriosis?	Diagnostic	NICE Guideline (modified)	Table App 15
9	Q5b	Diagnosis – Adenomyosis	What is the diagnostic performance of ultrasound and MRI in diagnosing adenomyosis?	Diagnostic	New	Table App 16
10	Q6	Systems that can guide treatment	Do staging systems to guide treatment in people with endometriosis improve patient outcomes?	Intervention	NICE Guideline (modified)	Table App 17
11	Q7a	Pharmacological management – Analgesics	In people with endometriosis or adenomyosis, are analgesics effective for managing endometriosis- or adenomyosis-associated pain?	Intervention	NICE Guideline (modified)	Table App 18
12	Q7b	Pharmacological management – Neuromodulators	In people with endometriosis or adenomyosis, are neuromodulators effective for managing endometriosis- or adenomyosis- associated pain?	Intervention	NICE Guideline (modified)	Table App 19
13	Q7c	Pharmacological management – Hormonal medical treatments	In people with endometriosis or adenomyosis, what is the effect of hormonal medical treatments on patient outcomes?	Intervention	NICE Guideline (modified)	Table App 20
14	Q8	Alternatives to pharmacological and surgical management	In people with endometriosis or adenomyosis, what alternatives to pharmacological and surgical management are effective for managing endometriosis- or adenomyosis- associated pain?	Intervention	NICE Guideline (modified)	Table App 21
15	Q9a	Surgical management	In people with endometriosis or adenomyosis, what is the effect of surgical treatment on patient outcomes?	Intervention	NICE Guideline (modified)	Table App 22
16	Q9b	Combination of surgery and hormonal treatment	In people with endometriosis or adenomyosis, do hormonal medical treatments before or after surgery improve patient outcomes?	Intervention	NICE Guideline (modified)	Table App 23
17	Q9c	Hysterectomy	In people with endometriosis or adenomyosis, what is the effect of hysterectomy on patient outcomes?	Intervention	NICE Guideline (modified)	Table App 24
18	Q10	Management strategies to enhance fertility	In people with endometriosis with and without infertility, what is the effect of hormonal and surgical treatments on fertility?	Intervention	NICE Guideline (modified)	Table App 25
19	Q11	Follow--up	In people with endometriosis who are asymptomatic, do follow-up interventions improve primary patient outcomes?	Intervention	New	Table App 26
20	Q12	Secondary prevention	In people who have received treatment for endometriosis, what interventions prevent the recurrence of endometriosis symptoms and lesions?	Intervention	New – but partly addressed in NICE Guideline	Table App 27

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; NA, not applicable; SR, systematic review.

Evidence selection criteria

When formulating the relevant evidence review questions, the EEWG specified the patients, intervention, comparison, and outcomes using PICO criteria (for intervention questions). PPO criteria were specified for prognostic questions and PIRD criteria were specified for diagnostic test accuracy. These criteria have been developed to assist with evidence selection for each research question.

PICO criteria define the following four elements in detail:

P – the target population

I – the intervention being considered

C – the appropriate comparator

O – the outcome of interest.

PPO criteria define the following three elements in detail:

P – the target population

P – the prognostic factor being considered

O – the outcome of interest.

PIRD criteria define the following four elements in detail:

P – the target population

I – the test being considered (index test)

R – the reference test (gold standard)

D – the diagnosis of interest.

The research questions and associated evidence selection criteria for the Australian Endometriosis Guideline are defined in **Appendix B**. The PICO/PPO/PIRD criteria are generally consistent with the criteria documented in the research protocols for the NICE Guideline (available in Appendix D of the NICE 2017 Full Guideline). Where deviations from the NICE evidence selection criteria were made by the EEWG, these are noted in the tables in **Appendix B** and were taken into consideration when developing/refining the literature search strings (**Appendix C**). In particular, the EEWG agreed on the inclusion of several subpopulations that were excluded from the NICE 2017 Guideline (refer to Table 2), such as people with endometriosis occurring outside the pelvis,[14] postmenopausal people with endometriosis, and pregnant people with endometriosis.

Of note, the categorisation of outcomes as 'critical' and 'important' in the NICE Guideline did not follow the standard GRADE approach. The outcomes selected for a review question were considered critical for decision-making in a specific context. For pragmatic reasons, the outcomes for each question in the Australian Endometriosis Guideline did not deviate materially from those of the NICE Guideline.

[14] Extrapelvic endometriosis is variably defined in the literature. Pelvic endometriosis often refers to lesions proximal to the uterus such us the ovaries, the fallopian tubes, the uterine ligaments, and the surrounding pelvic peritoneum, whereas the term 'extrapelvic endometriosis' is taken to mean other areas of the body, including the vagina, vulva, cervix and perineum, the urinary system, the gastrointestinal tract, the thoracic cavity including lung and pleura, extremities, skin, and central nervous system. That is, 'extrapelvic endometriosis' often appears to encompass 'extragenital pelvic endometriosis' (i.e. endometriotic lesions involving pelvic organs such as rectum, sigmoid, and bladder) plus endometriosis outside the pelvis.

Systematic literature review

Search strings

The literature searches predominantly used the search strings developed for the NICE 2017 Guideline, with additions or deletions to the search strings in accordance with the changes outlined in the evidence selection criteria, as agreed by the EEWG.

Literature search date restrictions are outlined in the evidence selection criteria tables in **Appendix B**. The majority of questions updated the NICE literature searches from December 2016 onwards. However, where populations, interventions or comparators were added to the evidence selection criteria, the literature searches for these new elements go back 10 years (i.e. from 2009 onwards). Likewise, the literature searches for the new research questions go back to database inception or the date proposed by the EEWG.

The search strings for each research question prioritised for systematic review/update are provided in **Appendix C**.

Literature search approach

The bibliographic databases that were searched for each research question are listed in the evidence selection criteria tables in **Appendix B**. For the majority of research questions, the literature searches include the Medline database (which includes articles ahead of print) and the EMBASE database. However, Q2a (type of information and support) also included a search of PsychINFO.

The reference lists of included studies were scanned for any additional relevant studies that might not have been identified in the formal literature searches. In addition, articles recommended by EEWG members were considered for inclusion if they met the pre-specified eligibility criteria.

Record management

For all research questions, records from the literature searches were downloaded into an EndNote database for de-duplication. Unique records were then uploaded into the systematic review software, DistillerSR, for screening.

Inclusion and exclusion criteria

Identified citations were assessed against inclusion/exclusion criteria based on the components of the PICO/PPO/PEO/PIRD criteria outlined in **Appendix B**. For example, the exclusion criteria for intervention questions were:

- wrong study type,
- wrong population,
- wrong intervention,
- wrong comparator,
- wrong outcomes.

Additional reasons for excluding articles were:

- non-human study,
- non-English language article,
- non-systematic (narrative) review, editorial, opinion piece or letter,
- conference abstract, or
- research protocol or systematic review protocol.

Screening

Records were screened and annotated in DistillerSR according to whether they were 'included', 'excluded' or 'uncertain'. In most cases, the screening of articles was based on the title and abstract. If the decision to include or exclude was not clear from the title or abstract (or if there is no abstract), full publications were retrieved. Any articles that did not clearly meet the inclusion or exclusion criteria were marked 'uncertain' for adjudication by the relevant EEWG subgroup.

Appendix D includes a summary of the total number of unique records identified from the literature searches for each research question, the total number of records screened at full text and the number of included studies. **Appendix D** also provides the citation details for all included studies, by research question.

Data extraction

Data from new included studies were extracted using a similar format and level of detail to that presented in the NICE 2017 Guideline.

Evidence appraisal

Consistent with the NICE 2017 Guideline, the new evidence was appraised using GRADE methodology. To facilitate comparison and/or synthesis of the old and new evidence, GRADE tables were prepared using a similar format to the NICE 2017 Guideline.

Meta-analysis was considered, where appropriate, to combine the results of intervention questions. Network meta-analysis of direct and indirect evidence was not performed due to resource limitations.

GRADEpro software was used to assess the quality of each outcome, taking into account individual study quality factors and the meta-analysis results. The quality elements considered using GRADE are:

- risk of bias (study limitations),
- inconsistency/coherence of findings,
- indirectness/applicability or relevance of findings,
- imprecision/theme saturation or sufficiency, and
- publication bias.

GRADE **Evidence Profile Tables** were generated to summarise the evidence by outcome and provide an overall summary of the quality of evidence for that outcome (referred to as the **GRADE rating**) for consideration by the EEWG.

As the GRADE toolbox is primarily designed for randomised controlled trials (RCTs) and observational studies, the quality assessment elements and outcome presentation for diagnostic accuracy and qualitative studies used a non-GRADE approach that is consistent with the NICE 2017 Guideline. For prognostic studies, summary tables were also prepared in a format similar to the NICE 2017 Guideline (with appraisal not based on the GRADE approach).

Summary of findings

GRADE **Evidence Summary Tables** were produced to compile the EEWG's assessments of clinical importance per outcome, alongside the evidence quality and the uncertainty in the effect estimate (imprecision). **Evidence Statements** were developed to summarise the key features of the clinical evidence presented, by outcome or theme. The Evidence Statements were worded in a manner similar to the NICE Evidence Statements.

Appendix A contains a summary of NICE evidence statements and recommendations for each of the NICE research questions.

Adoption or adaption of recommendations

The **GRADE-ADOLOPMENT** framework (or a variation of) was the preferred model for development of the Australian Endometriosis Guideline because the approach combines advice on adoption, adaptation and the creation of new recommendations. The framework provides a systematic approach to guideline adaptation, which helps to maintain methodological rigour and ensure that the recommendations stay true to the evidence, while taking local needs into account. The defined steps within the framework provide structure to the adaptation process and increase transparency so that the process followed and the rationale for the adapted guidance is clear. This transparency is also beneficial when it comes time to update the guideline.

The GRADE-ADOLOPMENT process required the completion of GRADE **Evidence-to-Decision frameworks** that incorporated the updated evidence synthesis with particular attention to the local healthcare setting and key context-specific factors (e.g. the balance of benefits and harms, acceptability and feasibility of the intervention). The Evidence-to-Decision framework comprised a structured summary of generic and specific issues considered by the EEWG and the key deliberations when formulating recommendations. The Evidence-to-Decision framework in the NICE 2017 Guideline used a different structure to that specified in the GRADEpro software. As such, the deliberations of the NICE guideline development Committee were manually mapped to the GRADEpro Evidence-to-Decision framework for consideration by the EEWG.

The source recommendations were adopted or adapted depending on agreement between the updated evidence synthesis and the original synthesis from the NICE 2017 Guideline. If no information or recommendation was available, a new recommendation was developed.

The availability of the original Evidence-to-Decision framework enabled decisions on whether new judgements of the evidence differed from the original assessment by the NICE Committee. This helped to determine whether the direction and strength of a recommendation had changed, and if so, whether the recommendation should be adapted accordingly.

Where substantial amendments to the wording of recommendations changed the meaning or the strength of the language used, the recommendation may no longer have reflected the NICE evidence base, in which case the designation of 'Committee Opinion' was considered more appropriate.

Development of new recommendations

New recommendations were drafted on the basis of the EEWG's interpretation of the available evidence, taking into account the balance of benefits and harms between different courses of action. The net benefit over harm (clinical effectiveness) was considered, focusing on the critical outcomes. The assessment of net benefit was moderated by the importance placed on the outcomes (the group's values and preferences) and the confidence the group had in the evidence (evidence quality).

When evidence was of poor quality, conflicting or absent, the EEWG drafted recommendations based on their expert opinion. The considerations for making consensus-based recommendations included the balance between potential harms and benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The EEWG also took into account the potential harm of failing to make a clear recommendation.

The wording of recommendations was agreed by the EEWG and reflects the 'strength' of the recommendation. A 'strong' recommendation applied to situations where the group believed that the benefits clearly outweighed the harms for most people. Similarly, a negative recommendation was used when the harms clearly outweighed the benefits for most people.

Economic considerations

Although *de novo* cost-effectiveness analyses were undertaken for the NICE 2017 Guideline to ensure that recommendations represented a cost-effective use of healthcare resources, the resourcing for the Australian Endometriosis Guideline did not cover *de novo* economic evaluation in the Australian setting. A decision was made by the EEWG to develop recommendations on the basis of the clinical evidence without specific consideration of the economic and financial implications of each recommendation.

Impact of the COVID-19 pandemic

Due to the large number of research questions and the COVID-19 pandemic, the EEWG were unable to meet face-to-face as originally planned. Instead, a series of 15 videoconferences (each of 1.5 hours duration) were held over the period from 03 March 2020 to 29 June 2020 with subgroups of the EEWG. The Organising Group allocated EEWG members into six subgroups, each comprised of five or six EEWG members with an interest or expertise in particular topics. Prior to each subgroup videoconference, members were provided with the relevant sections of the Full NICE Guideline together with the publications of any new primary studies identified in the literature search update. During Evidence-to-Decision deliberations, the subgroups considered the full body of evidence for a particular research question and developed draft recommendations that were subsequently circulated to the full EEWG for input, refinement and approval.

Findings of systematic update

Appendix D provides a list of citations for all included studies identified in the literature search update, by research question.

Q1 – Signs and symptoms

What are the signs and symptoms of endometriosis?

Description of clinical evidence

The literature search date was **16 October 2019**.

No relevant studies were identified in the literature search. Comparative cohort studies looking at signs and symptoms of endometriosis were identified. These studies were excluded due to the population being confirmed endometriosis; the study not performing multivariate analysis and/or not adjusting for confounders.

Q2a – Information and support

What information and support do people with endometriosis and their families find helpful?

Description of clinical evidence

The literature search date was 16 October 2019.

No new relevant studies were identified in the literature search.

Q3 – Timing of diagnosis and intervention

In people with suspected endometriosis, is early diagnosis and intervention beneficial?

Description of clinical evidence

The literature search date was **17 October 2019.**

No relevant studies were identified in the literature search. The majority of studies were excluded due to not looking at duration of symptoms as a prognostic factor. One comparative study looking at the impact of diagnostic delay was identified (Brandes et al. 2017) but excluded due to not adjusting for confounders.

Q5a – Diagnosis of endometriosis

What is the diagnostic performance of clinical examination, ultrasound, CT scan, MRI, biomarkers, and surgery in diagnosing endometriosis?

Description of clinical evidence

The literature search date was 16 October 2019.

Clinical evidence is summarised by intervention (index test) type, as classified in the Research Protocol:

- clinical examination

- ultrasound (transabdominal, transvaginal, rectal scanning)
- computed tomography (CT)
- pelvic magnetic resonance imaging (MRI)
- biomarkers (e.g. CA-125 [cut-off ≥35 U/mL], HE-4, PGP 9.5)
- surgical diagnosis with or without histological confirmation.

Clinical examination and CT are additional interventions that were not examined in the NICE 2017 Guideline. Clinical examination may be a 'pre-test' in some studies. For most studies, signs and symptoms and patient history are pre-tests but the nature of pre-testing is not well reported in the publications.

Studies were eligible for inclusion if the reference standard was surgical visualisation with histological confirmation. Eligible study participants were those with suspected (not confirmed) endometriosis on clinical grounds. The exception was for diagnosis of bowel involvement in people with a diagnosis of endometriosis. In these cases, identification of bowel lesions is generally used for the purposes of surgical planning, and the EEWG agreed that these studies would provide useful information. Studies of indirect populations (for example, all people undergoing laparoscopy) were excluded.

Case-control studies were not eligible for inclusion as the ability of a diagnostic test to discriminate cases from controls is different to differentiation of endometriosis from conditions with a similar presentation to endometriosis. Retrospective studies often use a case-control design and were excluded on that basis.

Studies that only reported a lesion-level analysis, rather than analysis at the participant level, were also excluded, as were studies that examined the relationship between visual markers (e.g. thickness of the uterine junctional zone) and confirmed endometriosis.

A total of 11 relevant SRs were identified in the literature search. An overview of the diagnostic techniques examined and compared in the identified SRs is shown in Table 4 (organised in reverse chronological order). None of the identified reviews could be adopted as the evidence base for any diagnostic test because of the different eligibility criteria between the published reviews and the Research Protocol (population, study design and reference standard), lack of formality in the data collection (some reviews were essentially narrative reviews of a range of diagnostic techniques with very little data extraction), and the inclusion of older studies in the published reviews.

Table 4 Overview of identified SRs examining the performance of diagnostic tests

Author, year	Clinical exam	Ultrasound	CT	MRI	Biomarkers	Surgical diagnosis	Site of endometriosis
Gao 2019					✓		endometriosis
Kiesel 2019		✓		✓	✓		endometriosis
Moga 2019					✓		endometriosis and ERONs
Moura 2019		✓		✓			rectosigmoid
Woo 2019			✓				bowel
Agrawal 2018					✓		endometriosis
Barra 2018	✓	✓	✓	✓			ureteral
Guerriero 2018		✓		✓			deep infiltrating
Li 2018					✓		endometriosis
Leone Roberti Maggiore 2017	✓	✓		✓			bladder
Guerriero 2016		✓					rectosigmoid

Abbreviations: CT, computed tomography; ERON, endometriosis-related ovarian neoplasm; MRI, magnetic resonance imaging.

A total of 24 relevant primary diagnostic studies were identified in the literature search. An overview of the diagnostic techniques examined and compared in the identified studies is shown in Table 5 (organised in reverse chronological order). No test-and-treat RCTs reporting quality of life outcomes for patients allocated to different diagnostic tests were identified.

The diagnostic performance outcomes specified in the Research Protocol are sensitivity, specificity and Area Under the Curve (AUC). Sensitivity and specificity are measures of the ability of a test to correctly classify a person as having or not having the condition. When **sensitivity** is high, a negative test result rules out the disorder. When **specificity** is high, a positive test result rules in the disorder. **AUC** (ROC data) shows the true positive rate (sensitivity) as a function of the false positive rate. The NICE 2017 Guideline interpreted AUC 0.71 – 0.80 to be 'moderate', AUC 0.81 – 0.90 to be 'good' and AUC 0.91 – 1.00 to be 'excellent or perfect'. An AUC <0.50 indicates that the index test is worse than chance.

Table 5 Overview of identified primary studies examining the performance of diagnostic tests

Author, year	Clinical exam	Ultrasound	CT	MRI	Biomarkers	Surgical diagnosis	Site of endometriosis
Berger 2019	✓	✓		✓			endometriosis & DIE
Chen 2019	✓	✓		✓			rectovaginal
Ferrero 2019a		✓					rectosigmoid
Ferrero 2019b		✓					rectosigmoid
Hernandez Gutierrez 2019		✓		✓			DIE
Rosefort 2019		✓					DIE with rectal involvement
Alborzi 2018		✓		✓			DIE
Mehedintu 2018			✓	✓			colorectal
Reid 2018		✓					rectal/ rectosigmoid
Yap 2018				✓			DIE
Ferrero 2017		✓	✓				rectosigmoid
Hirsch 2017					✓		endometriosis
Jiang 2017		✓					bowel
Leone Roberti Maggiore 2017		✓		✓			rectosigmoid
Ros 2017		✓					rectosigmoid
Young 2017		✓					DIE
Zannoni 2017		✓	✓				DIE
Baggio 2016	✓	✓	✓		✓		DIE with bowel involvement
Biscaldi 2014			✓	✓			sigmoid & rectal
Iosca 2013			✓				intestinal and ureteral
Stabile Ianora 2013			✓				rectosigmoid
Biscaldi 2011			✓				bowel endometriosis with ureteral involvement
Ferrero 2011		✓[a]	✓				rectosigmoid
Hudelist 2011	✓	✓[a]					DIE

Abbreviations: CT, computed tomography; DIE, deep infiltrating endometriosis; MRI, magnetic resonance imaging.
a Already included in the NICE 2017 Guideline for ultrasound (but not clinical exam).

Clinical examination

No relevant SRs that specifically examined the diagnostic performance of clinical examination were identified. However, one broad SR of ureteral endometriosis (Barra et al 2018) and one broad SR of bladder endometriosis (Leone Roberti Maggiore et al 2017) included sections on diagnosis that mentioned clinical history and examination.

Four relevant diagnostic studies were identified:

- Comparison of consecutive steps (history, clinical examination, dynamic TVUS, MRI) in the diagnosis of endometriosis and deep infiltrating endometriosis (DIE) (Berger et al 2019)
- Comparison of physical examination, TVS, MRI and rectal endoscopic sonography (RES) in the diagnosis of rectovaginal endometriosis (Chen et al 2019)
- Comparison of CT colonography (CTC) versus clinical history, serum CA 125 or TVS to detect bowel involvement in DIE (Baggio et al 2016)
- Comparison of TVUS versus clinical examination in the diagnosis of deep infiltrating endometriosis (DIE) (Hudelist et al 2011)

Ultrasound

Three new relevant SRs of the diagnostic performance of ultrasound were identified:

- Comparison of TVS vs MRI in the diagnosis of rectosigmoid endometriosis (Moura et al 2019)
- Comparison of TVS vs MRI in the diagnosis of DIE (Guerriero et al 2018)
- TVUS in the diagnosis of DIE of the rectosigmoid (Guerriero et al 2016)

One new 'broad' SR was identified that examined a range of less invasive tests (including TVUS) for the diagnosis of endometriosis (Kiesel et al 2019). In addition, one broad SR of ureteral endometriosis (Barra et al 2018) and one broad SR of bladder endometriosis (Leone Roberti Maggiore et al 2017) included sections on diagnosis that mentioned ultrasonography.

Fifteen relevant diagnostic studies were identified:

- Comparison of consecutive steps (history, clinical examination, dynamic TVUS, MRI) in the diagnosis of endometriosis and DIE (Berger et al 2019)
- Comparison of physical examination, TVS, MRI or rectal endoscopic sonography (RES) in the diagnosis of rectovaginal endometriosis (Chen et al 2019)
- TVS with and without bowel preparation in the diagnosis of rectosigmoid endometriosis (Ferrero et al 2019a)
- Rectal water contrast (RWC)-TVS with and without bowel preparation in the diagnosis of rectosigmoid endometriosis (Ferrero et al 2019b)
- Comparison of MRI versus TVUS in the diagnosis of DIE (Hernandez Gutierrez et al 2019)
- TVUS in the diagnosis of DIE and rectal involvement (Rosefort et al 2019)
- Comparison of MRI, TVUS or TRUS in the diagnosis of DIE (Alborzi et al 2018)
- TVS direct visualisation versus TVS 'sliding sign' or both in the diagnosis of rectal/rectosigmoid deep endometriosis (Reid et al 2018)
- Comparison of MRI versus rectal water-contrast TVS in the diagnosis of rectosigmoid endometriosis (Leone Roberti Maggiore et al 2017)

- Comparison of CT-colonography versus rectal water-contrast TVS in the diagnosis of rectosigmoid endometriosis (Ferrero et al 2017)
- Comparison of rectal water-contrast TVUS versus double-contrast barium enema in the diagnosis of bowel endometriosis (Jiang et al 2017)
- TVS with or without bowel preparation in the diagnosis of rectosigmoid DIE (Ros et al 2017)
- TVUS with bowel preparation in the diagnosis of DIE (Young et al 2017)
- Comparison of CT colonography versus clinical history, serum CA 125 or TVS to detect bowel involvement in DIE (Baggio et al 2016)
- Comparison of TVS versus CT-colonography with contrast media and urographic phase in the diagnosis of DIE (Zannoni et al 2017)

Two additional diagnostic studies were identified that compared ultrasound with other interventions: Ferrero et al (2011) compared multidetector CT enteroclysis with rectal water-contrast TVS in the diagnosis of rectosigmoid endometriosis; Hudelist et al (2011) compared TVUS with clinical examination in the diagnosis of DIE. Both these studies were included in the analysis of ultrasonography in the NICE 2017 Guideline. As such, the ultrasound data from these studies is not captured in the section below on ultrasound.

Computed tomography

One relevant SR of the diagnostic performance of CT was identified:

- CT in the diagnosis of bowel endometriosis (Woo et al 2019)

In addition, one broad SR of ureteral endometriosis (Barra et al 2018) included sections on diagnosis that mentioned CT.

Nine relevant diagnostic studies were identified:

- Comparison of CT-based virtual colonoscopy versus MRI or both in the diagnosis of colorectal endometriosis (Mehedintu et al 2018)
- Comparison of CT-colonography versus rectal water-contrast TVS in the diagnosis of rectosigmoid endometriosis (Ferrero et al 2017)
- Comparison of TVS versus CT-colonography with contrast media and urographic phase in the diagnosis of DIE (Zannoni et al 2017)
- Comparison of CT colonography versus clinical history, serum CA 125 or TVS to detect bowel involvement in DIE (Baggio et al 2016)
- Comparison of multidetector CT enema versus MRI enema in the diagnosis of sigmoid and rectal endometriosis (Biscaldi et al 2014)
- Multislice CT with colon water distension (MSCT-c) and intravenous iodinated contrast medium in the diagnosis of intestinal and ureteral endometriosis (Iosca et al 2013)
- CT water enema in the diagnosis of rectosigmoid endometriosis (Stabile Ianora et al 2013)
- MDCT enteroclysis urography using a split-bolus technique in the diagnosis of ureteral involvement in bowel endometriosis (Biscaldi et al 2011)
- Comparison of multidetector CT enteroclysis versus rectal water-contrast TVS in the diagnosis of rectosigmoid endometriosis (Ferrero et al 2011)

Magnetic resonance imaging

Two new relevant SRs were identified:

- Comparison of TVS vs MRI in the diagnosis of rectosigmoid endometriosis (Moura et al 2019)
- Comparison of TVS vs MRI in the diagnosis of DIE (Guerriero et al 2018)

One new 'broad' SR was identified that examined a range of less invasive tests (including MRI) for the diagnosis of endometriosis (Kiesel et al 2019). In addition, one broad SR of ureteral endometriosis (Barra et al 2018) and one broad SR of bladder endometriosis (Leone Roberti Maggiore et al 2017) included sections on diagnosis that mentioned MRI.

Eight new relevant diagnostic studies were identified:

- Comparison of consecutive steps (history, clinical examination, dynamic TVUS, MRI) in the diagnosis of endometriosis and DIE (Berger et al 2019)
- Comparison of physical examination, TVS, MRI or rectal endoscopic sonography (RES) in the diagnosis of rectovaginal endometriosis (Chen et al 2019)
- Comparison of MRI versus TVUS in the diagnosis of DIE (Hernandez Gutierrez et al 2019)
- Comparison of MRI, TVUS or TRUS in the diagnosis of DIE (Alborzi et al 2018)
- Comparison of CT-based virtual colonoscopy versus MRI or both in the diagnosis of colorectal endometriosis (Mehedintu et al 2018)
- MRI in the diagnosis of DIE (Yap et al 2018)
- Comparison of MRI versus rectal water-contrast TVS in the diagnosis of rectosigmoid endometriosis (Leone Roberti Maggiore et al 2017)
- Comparison of multidetector CT enema versus MRI enema in the diagnosis of sigmoid and rectal endometriosis (Biscaldi et al 2014)

Biomarkers

Six new relevant SRs and two new diagnostic studies were identified in the literature search and are outlined below according to type of biomarker.

In addition, another SR was identified that examined a range of "less invasive tests" (including genetic tests, biomarkers and miRNA) for the diagnosis of endometriosis (Kiesel et al 2019). The review concluded that "although several non-invasive tests show promising diagnostic potential, further research is required before they can be recommended in routine clinical care. The combination of low invasive tests may be the solution to a reliable low invasive diagnosis of endometriosis".

Hormonal biomarkers

One new relevant SR was identified:

- Hormonal biomarkers in the diagnosis of endometriosis (Gao et al 2019)

17 studies were included, looking at the following biomarkers: cytochrome P450 aromatase, serum prolactin, 17β-hydroxysteroid dehydrogenase, endometrial luteinizing hormone/human chorionic gonadotropin receptor, endometrial estrogen receptor-a, endometrial estrogen receptor-β and estrogen sulfotransferase. Of these studies, there was one additional potentially relevant study that was not identified in the literature search. This study was published in a Chinese journal that could not be retrieved.

Peripheral biomarkers

Two new relevant diagnostic studies were identified in the literature search and met the eligibility criteria:

- Serum CA 125 in the diagnosis of endometriosis (Hirsch et al 2017)
- Comparison of CT colonography versus clinical history, serum CA 125 or TVS to detect bowel involvement in DIE (Baggio et al 2016)

Tissue biomarkers

One new relevant SR was identified:

- Serum ICAM-1 in the diagnosis of endometriosis (Li et al 2018)

Of the nine studies included in Li et al (2018), four were case-control studies and the other five were published in Chinese journals that could not be retrieved. The authors concluded that "the diagnostic sensitivity was much higher in patients of Asian ethnicity [Chinese publications] compared with those of Caucasian ethnicity".

Urine biomarkers

No new relevant evidence was identified.

MicroRNAs (miRNAs)

Two new relevant SRs were identified:

- miRNAs as potential biomarkers in endometriosis (Agrawal et al 2018)
- miRNAs as potential biomarkers in endometriosis and endometriosis-related ovarian neoplasms (Moga et al 2019)

The Agrawal et al (2018) SR concluded the following: “Based on the literature overview, circulating miRNAs seem to be promising candidates for a non-invasive biomarker for endometriosis. However, considerable discovery is yet to be done in this domain, and the techniques for miRNA profiling need to be further explored and standardised. The current disagreement between various studies as to methodology and results warrants the need for larger, well-controlled, systematic validation studies, with uniformity in research approaches, and involving a myriad of patient populations.”

Likewise, the Moga et al (2019) SR concluded that, “Although multiple studies were conducted on endometriosis, no single miRNA was considered as a sole biomarker for this pathology. However, since the prognostic value of biomarkers is generally enhanced if more are assessed at the same time, a panel of miRNAs could be a better indicator of the disease. The seemingly conflicting results of different studies highlight the need for further extended research to prove if miRNAs could become viable biomarkers for endometriosis and endometriosis-related ovarian neoplasms.”

Surgical diagnosis

No new relevant diagnostic studies were identified.

Summary of included studies

Clinical examination

Table 6 Evidence Summary: Diagnosis of endometriosis – clinical examination

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 7)
Full citation Berger JP, Rhemrev J, Smeets M, Henneman O, English J, Jansen FW. Limited added value of magnetic resonance imaging after dynamic transvaginal ultrasound for preoperative staging of endometriosis in daily practice: a prospective cohort study. Ultrasound Med. 2019. 38:989-996. **Country** The Netherlands **Aim** To assess the added value of MRI after dynamic TVUS in the diagnostic pathway for preoperative staging of pelvic endometriosis. **Study type** Prospective **Study dates** 22 Apr 2014 to 1 May 2015 **Source of funding** Not stated	**Population** Patients with a clinical suspicion of endometriosis **Sample size** 274 subjects underwent conservative treatment according to ESHRE guidelines. 89 were selected for surgery, of whom **72** underwent the full diagnostic pathway: i.e. history, clinical examination, dynamic TVUS, and MRI. 81.9% DIE confirmed at surgery **Setting** Referral center for endometriosis **Subgroup analysis** DIE **Inclusion criteria** Clinical suspicion of endometriosis; selected for surgery and underwent the complete diagnostic pathway (i.e. history, clinical examination, dynamic TVUS, and MRI). **Exclusion criteria** Younger than age 18 years; dynamic TVUS not possible (e.g. Virgo condition); claustrophobia or contraindications to MRI.	Index test 1 History Index test 2 History + clinical exam Index test 3 History + clinical exam + dynamic TVUS (without BP) Index test 4 History + clinical exam + dynamic TVUS (without BP) + MRI (no BP, no contrast) Reference standard Visual diagnosis at laparoscopy with histological confirmation	The history included symptoms of dyspareunia, dysmenorrhoea, dysuria, dyschezia, and cyclic or CPP and subfertility. In addition, patients were questioned about the quality of their social life: i.e. physical discomfort and depression. Physical examinations were performed by 2 examiners, both with more than 15 years of experience in endometriosis. Based on the information obtained during the history and pelvic examination, a dynamic TVUS examination was performed by a single examiner with 5 years of specialisation in TVUS for endometriosis. MRI was performed within 6 weeks after dynamic TVUS. All MRI examinations were evaluated by a single radiologist with 10 years of experience in endometriosis, blinded to the results of the history, clinical examination, and dynamic TVUS. All patients included (n=72) underwent laparoscopic resection of all endometriosis. Staging of endometriosis was determined by 2 gynecologists on visual inspection at laparoscopy according to the revised American Fertility Society (AFS) criteria. All visual diagnosis of endometriosis was confirmed by histologic examination.	****No 2x2 data**** **Endometriosis** **History (n=72)** Sensitivity: 61.5% Specificity: 0% **History + clinical exam (n=72)** Sensitivity: 58.6% Specificity: 0% p-value NS compared to previous step **History + clinical exam + TVUS (n=72)** Sensitivity: 93.7% Specificity: 55.6% p<0.001 compared to previous step **History + clinical exam + TVUS + MRI (n=72)** Sensitivity: 85.9% Specificity: 62.5% p-value NS compared to previous step [15] **DIE** **History (n=72)** Sensitivity: 60.0% Specificity: 0% **History + clinical exam (n=72)** Sensitivity: 59.3% Specificity: 0% p-value NS compared to previous step	We conclude that routine MRI after dynamic TVUS has no added value based on the following lines of evidence: First, the results clearly show that for diagnosis of pelvic endometriosis, inclusion of dynamic TVUS alone performed as well as after MRI. Second, the same conclusion can be drawn for diagnosis of DIE. Third, dynamic TVUS performed even better at predicting the correct stage in patients predominantly affected by DIE. Our results clearly show that there is no substantial added value of routine MRI after dynamic TVUS for the preoperative staging of endometriosis. After the history and physical examination, dynamic TVUS and MRI both yield similar added value in preoperative staging of endometriosis with great overlap in clinical information. Both have their advantages and disadvantages, so choosing proper diagnostic imaging depends on the availability of an expert sonographer or MRI radiologist and on the anatomic site of interest based on the history and physical examination. Several limitations of our study need to be considered. First, different scoring systems are proposed to	Patient selection: **Unclear** Index Test: **Low** Reference Standard: **Unclear** Flow and Timing: **Unclear** Potential applicability/ directness issues: **Endometriosis patients who undergo surgery may have a different profile to those who do not; tertiary referral centre – more likely to see complex/severe cases; very experienced technicians; single centre** Overall risk of bias assessment: **High and small sample size**

[15] The added value of MRI compared to history + clinical exam was significant (p<0.001)

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 7)
			The diagnosis of DIE was made if one of the following criteria was met: hyperintense foci on the fat-suppressed T1-weighted images with corresponding hemorrhagic foci on T2-weighted images, areas of fibrosis in the pelvic region, distortion of normal anatomy without any other explanation, and discontinuation of normal fatty tissue between organs.	**History + clinical exam + TVUS (n=72)** Sensitivity: 93.2% Specificity: NN[16] p<0.001 compared to previous step **History + clinical exam + TVUS + MRI (n=72)** Sensitivity: 88.1% Specificity: NN p-value NS compared to previous step [17]	document TVUS findings regarding DIE …. Second, … the prevalence of DIE was particularly high, resulting in a particularly high rate of diagnosis by the clinical history and physical examination. This finding was inherent to the fact that the study was performed in a center with expertise in endometriosis. Another explanation … was that low-grade endometriosis was treated conservatively.	
Full citation Chen Y, Wang D, Guo C. Accuracy of physical examination, transvaginal sonography, magnetic resonance imaging, and rectal endoscopic sonography for preoperative evaluation of rectovaginal endometriosis. Ultrasound Quarterly. 2019. 35:54-60. **Country** China **Aim** To compare the effectiveness of physical examination, TVS, MRI, and rectal endoscopic sonography (RES) for the identification of rectovaginal endometriosis (RVE) and potential rectal infiltration **Study type** Retrospective	**Population** Patients with suspected RVE **Sample size** 29 consecutive patients 72.4% had rectovaginal endometriosis on histology, 52.4% had other endometriosis besides RVE **Setting** Department of Obstetrics and Gynecology at Shengjing Hospital of China Medical University **Subgroup analysis** Rectal infiltration **Inclusion criteria** Clinical suspicion or clinical evidence of RVE on the basis of associated symptoms (i.e. deep dyspareunia, CPP, periodically dyschezia, and rectal bleeding) and/or signs. **Exclusion criteria** Not reported.	Index test 1 Physical examination (bimanual and trimanual) Index test 2 TVS (without BP) Index test 3 Pelvic MRI with gadolinium-based contrast Index test 4 RES (with rectal lavage) Reference standard Surgical and histologic findings Prior tests Clinical history and physician's clinical findings	All women underwent a physical examination, TVS, pelvic MRI, and RES before surgery. The radiologists or sonographers were informed about the medical history and clinical manifestation but were completely blinded to the results of the physical examination and previous imaging diagnosis. All women underwent transvaginal surgery or laparotomy in hospital. Surgical and histologic findings were compared with preoperative findings. Rectovaginal endometriosis was clinically diagnosed when hyacinth, irregular and/or palpable painful nodule, thickness and/or cystic expansion was detected in posterior vaginal fornix, posterior vaginal wall, and/or rectovaginal septum during digital vaginal and rectovaginal examination. All bimanual examinations were performed by the same experienced gynecologist before the imaging examinations. TVS was performed by physicians or ultrasound technologists who had at	****No 2x2 data**** **Diagnosis of RVE** **Physical examination** Sensitivity: 95.2% (74.1, 99.8) Specificity: 62.5% (25.9, 89.8) **TVS** Sensitivity: 42.9% (22.6, 65.6) Specificity: 87.5% (46.7, 99.3) **MRI** Sensitivity: 90.5% (68.2, 98.3) Specificity: 87.5% (46.7, 99.3) **RES** Sensitivity: 81.0% (57.4, 93.7) Specificity: 75.0% (35.6, 95.5) **Identification of rectal infiltration** **TVS** Sensitivity: 26.7% (8.9, 55.2)	MRI is the main examination method for comprehensive preoperative assessment. MRI combined with physical examination may be the main objective method for selection of the surgical approach and operative planning. The main function of RES is further accurate evaluation of the rectal invasion of RVE lesions. Comprehensive application of various diagnostic methods for accurate preoperative assessment allows for maximal surgical removal of the lesions with minimum morbidity. Several limitations of our study should be discussed. First, our institution is a tertiary referral center for gynecologic cases, … so we evaluated the diagnostic efficacy in a population at high risk for RVE... . In addition, only 29 women with clinical evidence of RVE underwent imaging via all 3 techniques, contributing to the potential bias. …. Second, in this study, most patients underwent	Patient selection: **Unclear** Index Test: **Low** Reference Standard: **Low** Flow and Timing: **High** Potential applicability/ directness issues: **Rectovaginal endometriosis patients who undergo surgery may have a different profile to those who do not; tertiary referral centre – more likely to see complex/severe cases.** **Unclear if physical exam method is standard.** Overall risk of bias assessment:

[16] As a consequence of the observational design of the study and the selection criteria for surgery, only patients with DIE or a VAS of less than 7 underwent surgery; this approach explains why the specificity could not be calculated.

[17] The added value to MRI compared to history + clinical exam was significant (p<0.001)

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 7)
Study dates Mar 2010 to May 2017 **Source of funding** The authors declare no COI			least 10 years' experience in gynecologic imaging. Rectal endoscopic sonography was performed by physicians experienced in endoscopic sonography in RES for diseases of female low genital tract. All surgeries were performed by a professional team comprising gynecologic and colorectal surgeons with considerable experience in pelvic cavity operation. Histologic diagnosis of the excised specimens was made by pathologists experienced in identifying endometriosis, who were blinded to the imaging examination results.	Specificity: 85.7% (56.2, 97.5) **MRI** Sensitivity: 73.3% (44.8, 91.1) Specificity: 92.9% (64.2, 99.6) **RES** Sensitivity: 86.7% (58.4, 97.7) Specificity: 85.7% (56.2, 97.5)	nodulectomy …. Although the surgeons had extensive experience and attempted complete excision of RVE, possible incomplete surgical excision of rectovaginal septum nodules may lead to bias in the diagnosis of rectal invasion. Third, this was a retrospective cohort study.	**High and very small sample size**
Full citation Baggio S, Zecchin A, Pomini P, Zanconato G, Genna M, Motton M, Montemezzi S, Franchi M. The role of computed tomography colonography in detecting bowel involvement in women with deep infiltrating endometriosis: Comparison with clinical history, serum CA125, and transvaginal sonography. J Comp Assist Tomography. 2016. 40:886-891. **Country** Italy **Aim** To assess the diagnostic value of CTC in recognising bowel endometriosis in comparison with serum CA125, TVS, and presence of intestinal symptoms. **Study type** Prospective	**Population** Patients suspected of DIE enrolled to undergo surgical treatment **Sample size** 92 patients for CA125, TVS and intestinal symptoms; 37 patients for CTC. All were diagnosed with DIE and underwent laparoscopy; 53.3% had bowel endometriosis on surgery. **Setting** Gynecology Department of Borgo Trento Hospital **Subgroup analysis** None **Inclusion criteria** Reported CPP, dysmenorrhoea, dysuria, dyschezia, or dyspareunia; or a painful thickening or nodule in the uterosacral ligaments or in the vaginal cul-de-sac during vaginal examination. **Exclusion criteria** Not reported.	Index test 1 CA 125 >35 µg/mL Index test 2 TVS (without BP) Index test 3 CTC with BP and iodinated contrast Index test 4 Intestinal symptoms Reference standard Laparoscopic findings and subsequent pathological confirmation	One week before the operation, patients underwent the following evaluations: detailed history collection focusing on intestinal symptoms such as dyschezia (VAS ≥6), rectal tenesmus or cyclic constipation; CA125 serum testing (positive for value >35 µg/mL); and TVS. Dependent on availability of the Department of Radiology, CTC was performed on the same day. All surgical specimens were sent to anatomical pathology for conclusive diagnosis. DIE is defined by the presence of endometriosis lesions penetrating into the retroperitoneal space or the wall of pelvic organs to a depth of at least 5 mm.[18]	****2x2 available**** **Bowel involvement** **CA125** Sensitivity: 0.59 Specificity: 0.86 **TVS** Sensitivity: 0.41 Specificity: 0.93 **CTC** Sensitivity: 0.68 Specificity: 0.67 **Intestinal symptoms** Sensitivity: 0.67 Specificity: 0.56	CTC proved to be an accurate and low invasive imaging technique to detect DIE of the bowel and compared favorably with clinical evaluation, serum CA125 determination, and TVS for recognition of bowel endometriosis implants. Clinical history and physical examination are obviously not enough. Some patients with rectal involvement did not complain of abdominal symptoms….. On the opposite, some patients may complain of symptoms in the absence of bowel implants when severe endometriosis and chronic inflammation extensively involve the pelvis causing CPP. In our study, the PPV of CA125 was high, but the sensitivity was not satisfactory enough to give the test the accuracy we were looking for. Our study had several limitations, the major being the limited experience in recognising bowel endometriosis of both the	Patient selection: **Unclear** Index Test: **Low** Reference Standard: **Unclear** Flow and Timing: **Low** Potential applicability/ directness issues: **DIE patients who undergo surgery may have a different profile to those who do not undergo surgery, and those who do not have DIE; single centre.** **Unclear if intestinal symptoms is representative of clinical exam.** Overall risk of bias assessment: **High (and small sample size for CTC)**

[18] This definition is taken from the publication introduction, not the methods section.

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 7)
Study dates Jan 2014 to Jun 2015 **Source of funding** No funding from any organisation; the authors declare no COI					gynecologists who made the TVS and the radiologists who made the CTC.	
Full citation Hudelist G, Ballard K, English J, Wright J, Banerjee S, Mastoroudes H, Thomas A, Singer CF, Keckstein J. Transvaginal sonography vs. clinical examination in the preoperative diagnosis of deep infiltrating endometriosis. Ultrasound Obstet Gynecol. 2011. 37:480-487. **Country** UK and Austria **Aim** To compare the diagnostic performance of clinical vaginal examination with that of TVS in the presurgical diagnosis of DIE **Study type** Prospective **Study dates** Not reported **Source of funding** Not reported	**Population** Women with suspected endometriosis **Sample size** 129 women 64% had histological confirmation of endometriosis; 40% of whom had DIE **Setting** Pelvic pain clinics, two UK-based (Worthing and Chertsey HS Hospital) and one Austrian (Centre for Endometriosis, Villach) **Subgroup analysis** Location of endometriosis **Inclusion criteria** Premenopausal women referred to the pelvic pain clinic for laparoscopy because of suspected endometriosis based on clinical history and the referring physician's clinical findings; or self-referred women (coming to the pain clinic without having seen any gynecologist before for their current problems). **Exclusion criteria** History of gynecological cancer, previous surgery for DIE or other disease entities requiring resection of the bladder, and/or dissection of the rectovaginal space and/or anterior rectosigmoidal wall; congenital anatomical	Index test 1 Clinical (vaginal) examination Index test 2 TVS (without BP) Reference standard Histologically confirmed endometriosis	Vaginal examination was performed by one of five experienced clinical examiners who were all blinded to TVS results. Vaginal examination was undertaken prior to TVS. The bimanual per vaginam examination was considered positive and therefore suggestive of endometriotic infiltration if the following criteria were met: palpable nodule or thickened area or a palpable cystic expansion with topographic-anatomical correlation to the following sites: left and/or right USLs, vagina, rectovaginal space, pouch of Douglas, the rectosigmoid and the urinary bladder (posterior wall). TVS was carried out with either a Logic 9 (GE Healthcare Ultrasound) or Accuvix XQ (Accuvix Sonoace, Medison Co., Ltd,) scanner using a 5–9-MHz transducer for transvaginal visualisation of the urinary bladder, both adnexa, the uterus, the vagina and rectovaginal space, the USLs and the rectosigmoid. The bowel was not prepared prior to investigation. All TVS scans were performed by one examiner who was blinded to the results of the vaginal examinations but was aware that the women were being investigated for CPP and therefore endometriosis was suspected. All patients included in the study underwent laparoscopy and, histological confirmation of endometriosis. In accordance with previous studies, DIE was defined as	****2x2 in text?**** **Ovary** **Clinical exam** Sensitivity: 41% (22, 61) Specificity: 99% (95, 100) **TVS** Sensitivity: 96% (81, 100) Specificity: 96% (90, 99) **USLs** **Clinical exam** Sensitivity: 50% (31, 69) Specificity: 80% (71, 87) **TVS** Sensitivity: 63% (44, 80) Specificity: 98% (93, 100) **Pouch of Douglas** **Clinical exam** Sensitivity: 76% (53, 92) Specificity: 92% (85, 96) **TVS** Sensitivity: 76% (53, 92) Specificity: 100% (95, 100) **Vagina** **Clinical exam** Sensitivity: 73% (39, 94) Specificity: 98% (94,	Taken together, our results strongly suggest that vaginal examination alone may be insufficient to detect endometriosis prior to laparoscopy. The use of TVS, performed by well-trained staff clearly enhances diagnostic accuracy, especially in patients with cystic endometriosis of the ovaries or DIE of the uterosacral ligaments bladder and rectosigmoid, but appears to be equally efficient in cases of DIE of the vagina and pouch of Douglas. Based on these data and the availability of TVS and vaginal examination, TVS can be recommended as the method of choice for the primary and preoperative assessment of pelvic pain patients with suspected endometriosis. In centers where TVS is not used on a routine basis, it should be included in the standard assessment of patients with pelvic pain.	Patient selection: **Unclear** Index Test: **Low** Reference Standard: **High** Flow and Timing: **Unclear** Potential applicability/ directness issues: **Endometriosis patients who undergo surgery may have a different profile to those who do not.** **Unclear if vaginal exam is representative of clinical exam in practice.** Overall risk of bias assessment: **High**

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 7)
	abnormalities of the genital tract; patient was a virgin (exclusion for performance of TVS).		subperitoneal endometriotic infiltration of tissues >5 mm. A total of three surgeons performed the laparoscopy, all with more than 10 years' experience in radical laparoscopic surgery for DIE. Surgeons were blinded to the results of the vaginal examination and TVS in one of the centres, but were aware of the vaginal examination and TVS results in the other two centers.	100) **TVS** Sensitivity: 64% (31, 89) Specificity: 99% (95, 100) **Rectovaginal space** **Clinical exam** Sensitivity: 78% (40, 97) Specificity: 98% (94, 100) **TVS** Sensitivity: 78% (40, 97) Specificity: 100% (96, 100) **Urinary bladder** **Clinical exam** Sensitivity: 25% (00, 81) Specificity: 100% (96, 100) **TVS** Sensitivity: 50% (07, 93) Specificity: 98% (94, 100) **Rectosigmoid** **Clinical exam** Sensitivity: 39% (22, 58) Specificity: 97% (93, 100) **TVS** Sensitivity: 90% (74, 98) Specificity: 99% (94, 100)		

Abbreviations: BP, bowel preparation; CA 125, serum Cancer Antigen 125; COI, conflict of interest; CPP, chronic pelvic pain; CTC, computed tomography colonography; DIE, deep infiltrating endometriosis; ESHRE, European Society of Human Reproduction and Embryology; MRI, magnetic resonance imaging; NN, not a number; NS, not significant; RES, rectal endoscopic sonography; RVE, rectovaginal endometriosis; TVS, transvaginal sonography; TVUS, transvaginal ultrasound; USL, uterosacral ligaments; VAS, visual analogue scale.

Table 7 QUADAS-2 Diagnostic accuracy checklist: Diagnosis of endometriosis – clinical examination

Domain	Question	Berger et al 2019	Chen et al 2019	Baggio et al 2016	Hudelist et al 2011
Patient selection					
Signalling questions	Was a consecutive or random sample of patients enrolled?	Unclear (information not reported and decision on patient selection for MRI is unclear)	Yes	Unclear (information not reported and decision on patient selection for CTC is unclear)	Unclear (information not reported)
	Was a case-control design avoided?	Yes	Yes	Yes	Yes
	Did the study avoid inappropriate exclusions?	Yes	Unclear (not reported)	Unclear (not reported)	Yes
Risk of Bias	**Could the selection of patients have introduced bias?**	**Unclear**	**Unclear**	**Unclear**	**Unclear**
Concerns regarding applicability	Are there concerns that the included patients and setting do not match the review question?	High (tertiary referral centre – more likely to see complex/severe cases; very experienced technicians; single centre)	High (tertiary referral centre – more likely to see complex/severe cases)	Unclear (single centre)	Unclear
Index Test					
Signalling questions	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes[19]	Yes	Yes	Yes
	If a threshold was used, was it pre-specified?	N/A	N/A	Yes for CA125 N/A for other tests	N/A
Risk of bias	**Could the conduct or interpretation of the index test have introduced bias?**	**Low**	**Low**	**Low**	**Low**
Concerns regarding applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear (consecutive steps rather than individually; tertiary referral centre with very experienced technicians/clinicians performing the tests)	Unclear (physical examination (digital vaginal and rectovaginal examination); tertiary referral centre with very experienced technicians/clinicians performing the tests	Unclear (intestinal symptoms may not equate to 'clinical examination')	Unsure (vaginal examination)
Reference Standard					
Signalling questions	Is the reference standard likely to correctly classify the target condition?	Yes	Unclear (criteria for diagnosis not reported, however very experienced surgeons and pathologists)	Unclear (criteria for diagnosis not reported)	Yes

[19] Note consecutive index tests, therefore subsequent index tests had knowledge of previous index test results

Domain	Question	Berger et al 2019	Chen et al 2019	Baggio et al 2016	Hudelist et al 2011
	Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear (information not reported)	Yes	Unclear (information not reported)	Yes in one centre; No in other two centres[20]
Risk of Bias	**Could the reference standard, its conduct, or its interpretation have introduced bias?**	**Unclear**	**Low**	**Unclear**	**High**
Concerns regarding applicability	Are there concerns that the target condition as defined by the reference standard does not match the question?	High (high prevalence of DIE and not all patients with endometriosis undergo surgery)	High (only RVE not all patients with endometriosis undergo surgery)	High (only DIE)	High (not all patients with endometriosis undergo surgery)
Flow and Timing					
Signalling questions	Was there an appropriate interval between index test and reference standard?	Unclear (timeframe not reported)	Unclear (timeframe not reported)	Yes (1 week)	Unclear (timeframe not reported)
	Did all patients receive a reference standard?	Yes	Yes	Yes	Yes
	Did all patients receive the same reference standard?	Yes	No (all subjects underwent transvaginal surgery or laparotomy)	Yes	Yes
	Were all patients included in the analysis?	Yes	Yes	Yes	Yes
Risk of Bias	**Could the patient flow have introduced bias?**	**Unclear**	**High**	**Low**	**Unclear**

Abbreviations: CA, cancer antigen; CTC, computed tomography colonography; DIE, deep infiltrating endometriosis; MRI, magnetic resonance imaging; RVE, rectovaginal endometriosis; TVUS, transvaginal ultrasound.

[20] test accuracies of the double- vs. triple-blinded setting were compared to evaluate a possible review bias of the surgeon if aware of presurgical TVS and/or vaginal examination findings. However, no significant differences in test accuracies (Fisher's exact test) could be observed.

Ultrasound

Transvaginal ultrasound

Table 8 Evidence Summary: Diagnosis of endometriosis – transvaginal ultrasound

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 9)
Full citation Berger et al. 2019 **Country** The Netherlands **Study type** Prospective *See Table 6*	**Population** Patients with a clinical suspicion of endometriosis **Sample size** 72 underwent the full diagnostic pathway: i.e. history, clinical examination, dynamic TVUS, and MRI. 81.9% DIE confirmed at surgery *See Table 6*	Index test 1 History Index test 2 History + clinical exam Index test 3 History + clinical exam + dynamic TVUS (without BP) Index test 4 History + clinical exam + dynamic TVUS (without BP) + MRI (no BP, no contrast) Reference standard Visual diagnosis at laparoscopy with histological confirmation	Based on the information obtained during the history and pelvic examination, a dynamic TVUS examination was performed by a single examiner with 5 years' specialisation in TVUS for endometriosis, using a transvaginal transducer at a frequency of 5–9 MHz (Voluson E8; GE Healthcare). No bowel preparations or vaginal contrast agents were used; the bladder needed to be partially filled. First, a standard evaluation of the uterus and ovaries was performed. Then, the dynamic examination: uterine sliding sign, tenderness-guided US, evaluation of hard and soft markers. *See Table 6*	****No 2x2 data**** **Endometriosis** **History + clinical exam + TVUS (n=72)** Sensitivity: 93.7% Specificity: 55.6% p-value (compared to history + clinical exam): <0.001 **DIE** **History + clinical exam + TVUS (n=72)** Sensitivity: 93.2% Specificity: NN[21] p-value (compared to history + clinical exam): <0.001 *See Table 6 for other tests*	*See Table 6*	Overall risk of bias assessment: **High and small sample size** *See Table 6*
Full citation Chen et al. 2019 **Country** China **Study type** Retrospective *See Table 6*	**Population** Patients with suspected RVE **Sample size** 29 consecutive patients. 72.4% had RVE on histology, 52.4% had other endometriosis besides RVE *See Table 6*	Index test 1 Physical examination Index test 2 TVS (without BP) Index test 3 Pelvic MRI with gadolinium-based contrast agent Index test 4 RES (with rectal lavage)	TVS was performed with a Voluson 730 scanner (GE Healthcare) using a 5- to 9-MHz multifrequency transvaginal probe. No bowel preparation was performed. Physicians or ultrasound technologists had at least 10 years of experience in gynecologic imaging. The presence of rectovaginal nodules or lesions was determined by the operators, who simultaneously focused on the relationship with the adjacent anterior or lateral wall of the rectum. Thickening and/or the presence of an irregular hypoechoic cystic or noncystic mass within the	****No 2x2 data**** **Diagnosis of RVE TVS (n=29)** Sensitivity: 42.9% (22.6, 65.6) Specificity: 87.5% (46.7, 99.3) **Identification of rectal infiltration TVS (n=29)** Sensitivity: 26.7% (8.9, 55.2) Specificity: 85.7% (56.2, 97.5)	*See Table 6*	Overall risk of bias assessment: **High and very small sample size** *See Table 6*

[21] As a consequence of the observational design of the study and the selection criteria for surgery, only patients with DIE or a VAS of less than 7 underwent surgery; this approach explains why the specificity could not be calculated.

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 9)
		Reference standard Surgical and histologic findings Prior tests Clinical history and physician's clinical findings	retrocervical area or the rectovaginal septum was considered positive.	*See Table 6 for other tests*		
Full citation Ferrero S, Scala C, Stabilini C, Vellone VG, Barra F, Leone Roberti Maggiore U. Transvaginal sonography with vs without bowel preparation in diagnosis of rectosigmoid endometriosis: prospective study. Ultrasound Obstet Gynecol. 2019a. 53:402-409. **Country** Italy **Aim** To assess whether BP improves the diagnostic accuracy of TVS in detecting rectosigmoid endometriosis (RE). **Study type** Prospective **Study dates** Oct 2016 to Apr 2018 **Source of funding** Not reported.	**Population** Consecutive patients referred for symptoms of pelvic pain and/or suspicion of endometriosis **Sample size** 262 prospectively recruited and analysed. 45.0% had rectosigmoid endometriosis on surgery, 51.9% had endometriosis without rectosigmoid endometriosis, 3% did not have endometriosis **Setting** Tertiary referral centre for the treatment of endometriosis **Subgroup analysis** None **Inclusion criteria** Women of reproductive age; referred to the institution for the first time; symptoms of pelvic pain for >6 months and/or suspicion of endometriosis; laparoscopy within 6 months following TVS with BP. **Exclusion criteria** Previous diagnosis of colorectal endometriosis; previous intestinal surgery (other than appendectomy); previous hysterectomy or bilateral ovariectomy; intact hymen; TVS could not be performed.	Index test 1 2D-TVS with BP Index test 2 2D-TVS without BP Reference standard Laparoscopic surgery with histological confirmation Prior tests Symptoms and clinical examination	All subjects underwent TVS without BP and were requested to undergo TVS with BP within 1 wk to 3 months (mean 4.9 wks). For TVS with BP, a standardised protocol was followed: low-residue diet on the 3 days before TVS, oral laxative the night before TVS, and rectal enema within a few hours before TVS. All examinations performed by 2 gynecologists with extensive experience in sonographic diagnosis of endometriosis, informed of clinical history and symptoms but blinded to vaginal examination results. One consultant performed TVS without BP and the other independently performed TVS with BP. No distension of the rectum or vagina with contrast medium was used. 2D-TVS was performed using a Voluson E6 or S8 machine (GE Healthcare Ultrasound) according to a standardised protocol. Presence of rectosigmoid endometriosis was defined as lesions reaching at least the intestinal muscularis propria. Findings of TVS with and without BP were compared with surgical and histological findings. Rectosigmoid specimens were evaluated in a standardised way; depth of infiltration of endometriosis was assessed on the basis of the most luminal anatomical structure involved.	****2x2 available**** **Presence of rectosigmoid endometriosis (n=262)** **2D-TVS with BP** Sensitivity: 90.7 (83.9, 95.3) Specificity: 95.8 (91.2, 98.5) **2D-TVS without BP** Sensitivity: 88.1 (80.9, 93.4) Specificity: 95.8 (91.2, 98.5)	BP does not improve accuracy of non-enhanced TVS in diagnosing rectosigmoid endometriosis. Further studies should evaluate whether BP should be used when rectosigmoid distention with water and/or gel is used during TVS. Although the BP protocol may appear more extensive than that commonly used in clinical practice, it was chosen in order to perform TVS in ideal conditions of bowel cleansing. In line with this, BP was judged to be excellent or good by the sonographers in 97.7% of the patients. However, this optimal BP did not improve the diagnostic performance of TVS. This study was performed in a referral center for the treatment of endometriosis, and the high prevalence (45.0%) of rectosigmoid endometriosis in the study population represents a bias of the study. Therefore, the results cannot be extrapolated to the general population of women with clinical suspicion of deep endometriosis. Another limitation of the study is that TVS examinations were performed by expert sonographers, therefore we cannot dismiss the possibility that BP may affect the diagnostic performance of TVS carried out by less experienced sonographers. Patients included in this study underwent surgery because of	Patient selection: **Low** Index Test: **Low** Reference Standard: **High** Flow and Timing: **Low** Potential applicability/ directness issues: **Not all cases undergo surgery; referral centre more likely to see complex/ severe cases; BP protocol more extensive than in practice; single centre.** Overall risk of bias: **High**

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 9)
			Surgical procedures were performed by an experienced laparoscopic surgeon; a colorectal surgeon participated when bowel surgery was required. Laparoscopic surgery was performed to excise all visible endometriotic lesions (except diaphragm). After adhesiolysis, the rectosigmoid was inspected systematically to verify the presence and characteristics of endometriotic lesions.		persistence of pain symptoms and intestinal complaints, despite widespread use of hormonal therapies;… the results cannot be extrapolated to the whole population of patients who do not require surgical treatment of endometriosis.	
Full citation Ferrero S, Barra F, Stabilini C, Vellone VG, Leone Roberti Maggiore U, Scala C. Does bowel preparation improve the performance of rectal water contrast transvaginal ultrasonography in diagnosing rectosigmoid endometriosis. J Ultrasound Med Gynecol. 2019b. 38:1017-1025. **Country** Italy **Aim** To compare the performance of RWC-TVS with and without BP in diagnosing RE. **Study type** Prospective **Study dates** Not reported **Source of funding** Not reported.	**Population** Patients referred for symptoms suggestive of endometriosis **Sample size** 167 participants, 9 did not undergo surgery, 3 lost to FU, 155 underwent surgery and were included. 59.4% had rectosigmoid endometriosis at surgery, 40.6% had no rectosigmoid endometriosis **Setting** Tertiary referral centre for the treatment of endometriosis **Subgroup analysis** None **Inclusion criteria** Women of reproductive age; referred to the institution with pain symptoms and intestinal complaints suggestive of endometriosis, and suspicion of DIE at vaginal and rectal examinations. **Exclusion criteria** Previous surgical or radiological diagnosis of bowel endometriosis, previous hysterectomy, previous bilateral	Index test 1 2D-RWC-TVS with BP Index test 2 2D-RWC-TVS without BP Reference standard Laparoscopic surgery with histological confirmation Prior tests Vaginal and rectal examination	Participants underwent 2 RWC-TVSs within an interval of 1 week to 2 months (mean 4.4 weeks) using a Voluson E6 or S8 machine (GE Healthcare). RWC-TVSs were performed independently by 2 gynecologists with extensive experience in diagnosis of DIE, informed of the patients' clinical history and symptoms, but blinded to the results of the vaginal and rectal examination and the other RWS-TVS. Participants underwent laparoscopy within 6 months from the second RWC-TVS. The BP was a low-residue diet in the 2 days before the examination and a rectal enema administered a few hours before the exam. The rectosigmoid nodules appear as a thickening of the hypoechoic muscular layer or as hypoechoic nodules, with or without hyperechoic foci with blurred margins. Results were compared with surgical and histologic findings. Mean 15.6 weeks interval between RWC-TVS+BP and surgery. The surgeons were aware of the findings of RWC-TVS with and without BP. Furthermore, during the preoperative workup, some patients underwent other radiological examinations including multidetector	****No 2x2 data**** **Presence of rectosigmoid endometriosis (n=155)** **2D-RWC-TVS without BP** Sensitivity: 88.0 (79.6, 93.9) Specificity: 90.5 (80.4, 96.4) **2D-RWC-TVS with BP** Sensitivity: 91.3 (83.6, 91.2) Specificity: 88.9 (78.4, 95.4)	This prospective study shows that adding BP to RWC-TVS does not increase the performance of this examination in diagnosing rectosigmoid endometriosis and in assessing the characteristics of these nodules. When intestinal endometriosis is suspected, patients may immediately undergo RWC-TVS if the gynecologist has expertise in performing ultrasonography for DIE without the need to postpone the examination because of BP. In addition, patients may avoid the discomfort caused by BP, which may be more severe in women who already have intestinal complains. Finally, the cost of BP can be saved. It is possible that if RWC-TVS is performed by less experienced operators, BP has a different impact on the diagnostic performance of this exam. A theoretical limitation of this study is that the surgeons were aware of the findings of RWC-TVS with and without BP; however, it seems unlikely that this may have influenced the surgical findings.	Patient selection: **Unclear** Index Test: **Low** Reference Standard: **High** Flow and Timing: **Low** Potential applicability/ directness issues: **Not all cases undergo surgery; referral centre more likely to see complex/ severe cases; single centre.** Overall risk of bias: **High**

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 9)
	ovariectomy, virgin patients, or patients in whom TVS could not be performed.		computerised tomography enema, magnetic resonance enema, and computed tomographic colonography.			
Full citation Rosefort A, Huchon C, Estrade S, Paternostre A, Bernard J-P, Fauconnier A. Is training sufficient for ultrasound operators to diagnose deep infiltrating endometriosis and bowel involvement by transvaginal ultrasound? J Gynecol Obstet Hum Reprod. 2019. 48:109-114. **Country** France **Aim** To assess and compare the diagnostic accuracy of TVUS by trained or untrained ultrasound operators in DIE imaging, for diagnosing DIE and bowel involvement. **Study type** Prospective (retrospective?) **Study dates** 01 Oct 2004 to 30 Apr 2011 **Source of funding** The authors declared no COIs.	**Population** Patients with clinically suspected DIE **Sample size** 175 underwent surgery, 60 did not meet eligibility, 115 patients were included. 86.9% had posterior DIE, 34% had bowel involvement **Setting** Gynaecology surgery unit at a hospital **Subgroup analysis** DIE Rectal DIE **Inclusion criteria** Patients with symptoms advocating endometriosis at preoperative examination with no obvious pathology; painful symptoms were CPP >6 months duration, including severe dysmenorrhoea, deep dyspareunia, cyclic pelvic pain and painful defecation, with or without infertility; undergoing surgery. **Exclusion criteria** Myoma or an ovarian cyst (including endometrioma) of more than 40 mm; previously undergone surgery for the resection of a DIE nodule; without an available complete preoperative US report.	Index test 1 2D-TVUS (without BP) by trained operator Index test 2 2D-TVUS (without BP) by untrained operators Reference standard Surgical and histological criteria Prior tests Preoperative examination	TVUS operators were blind to the results of other imaging tests at the time of the TVUS. Surgeons were trained in endometriosis surgery and aware of the results of imaging tests performed before surgery. Surgical reports were based on ASRM classification. DIE was diagnosed according to surgical and histological criteria. A positive surgical diagnosis was based on obvious retroperitoneal infiltration of more than 5 mm, visible nodule or infiltration associated with palpable induration, or visible dark blue nodule of the posterior vaginal fornix. All TVUS operators had a national degree in gynecological US and regularly practiced. 46 operators were classified as untrained in endometriosis imaging based on their replies to a questionnaire. One operator was an obstetrician gynecologist who had practiced gynecologic and obstetrical US for over 15 years. This trained operator used a Voluson 730 Expert machine (GE Healthcare) with a 7-MHz transvaginal probe. Patients received a single TVUS by the trained (59/115) or an untrained operator (45/115), or received TVUS from both successively (11/115).	****2x2 available**** **Diagnosis of DIE** **Trained operator (n=70)** Sensitivity: 58% (95% CI 46, 70) Specificity: 87.5% (95% CI 63, 100) **Untrained operator (n=56)** Sensitivity: Not calculated Specificity: Not calculated **Diagnosis of rectal DIE** **Trained operator (n=70)** Sensitivity: 40% (95% CI 23, 59) Specificity: 93% (95% CI 86, 100) **Untrained operator (n=56)** Sensitivity: Not calculated Specificity: Not calculated	TVUS is not sufficient to diagnose DIE and bowel involvement, in particular when performed by untrained US operators. Our study is the first one to examine how the level of training of US operators affects the accuracy of TVUS for the diagnosis of DIE, according to well-defined criteria for training in endometriosis imaging. There are nonetheless several limitations to our study. At first, the prevalence of DIE was very high in our population suggesting the possibility of referral bias. Secondly, untrained US operators performed ''first-line'' US scans whereas the trained US operator performed first or second line scans on those patients who have been referred specifically to them: the indications for TVUS in these patients may be better defined and they probably have more severe endometriosis than patients sent for first-line scans. Finally, we assessed the diagnostic accuracy of TVUS by only one trained ultrasound operator, compared with many untrained ultrasound operators.	Patient selection: **High** Index Test: **High** Reference Standard: **High** Flow and Timing: **Unclear** Potential applicability/ directness issues: **Not all cases undergo surgery; single centre** Overall risk of bias: **High**
Full citation Alborzi S, Rasekhi A, Shomali Z, Madadi G, Alborzi M, Kazemi M, Hosseini Nohandani A. Diagnostic accuracy of	**Population** Consecutive patients with signs and symptoms of endometriosis **Sample size** 317 enrolled	Index test 1 2D-TVUS with BP Index test 2 TRS with BP Index test 3 MRI with contrast	All participants underwent MRI, TRS and TVS before surgery. All TVS was performed after bowel prep, by a single gynaecologic ultrasonographer with 30 years' experience, blinded to clinical findings,	****2x2 available**** **All DIE lesions (n=317)** **TVS** Sensitivity: 83.3% Specificity: 46.1%	In this large series of patients with symptoms of infiltrative endometriosis, we found that the diagnostic accuracy of MRI was higher than TVS and TRS in diagnosis	Patient selection: **Low** Index Test: **Low** Reference Standard: **High**

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 9)
magnetic resonance imaging, transvaginal, and transrectal ultrasonography in deep infiltrating endometriosis. Medicine. 2018. 97:8(e9536). **Country** Iran **Aim** To determine the diagnostic accuracy of MRI, TRS, and TVS in patients with DIE. **Study type** Prospective **Study dates** Mar 2013 to Feb 2015 **Source of funding** The authors declared no COIs.	79.5% had DIE, 20.5% had no lesion. **Setting** Private clinics and Mother and Child hospital, a tertiary healthcare centre affiliated with a university **Subgroup analysis** DIE Location of endometriosis **Inclusion criteria** Virgin patients referred with primary impression of endometriosis, based on clinical symptoms (CPP, dyspareunia, dysmenorrhoea) and physical examination (localised tenderness in posterior cul-de-sac or uterosacral ligament; palpable tender nodules in retrocervical position; tender enlarged adnexal mass). **Exclusion criteria** Claustrophobia, renal failure or other contraindication for gadolinium contrast medium injection; malignancy; history of any metallic implants or prostheses preventing MRI study; structural anomalies of the reproductive system; pregnancy; refusal or lack of compliance.	Reference standard Laparoscopy with histological examination Prior tests Clinical symptoms and physical examination	using a 7.5 MHz probe (Ultrasonix OP machine). The examination protocol comprised visualisation compartments, of the peritoneum and structures in the anterior and posterior as well as the uterus and ovaries. All TRS was performed using a 7.5 MHz linear probe (UltrasonixOP), 2 weeks after TVS, by a single gynaecologist blinded to clinical findings, following bowel prep. The examination protocol was similar to TVS and the same diagnostic criteria were applied. All MRI evaluations were reported by a certified radiologist with MRI fellowship, blinded to history and physical examination. MRI was performed before and after injection of gadolinium contrast medium using 1.5 Tesla (Avento Seimens Machine) through the body pelvic but not endovaginal coil, with lubricant gel inserted into the vaginal cuff and hyoscine intramuscular injection for better delineation. All operative laparoscopy interventions were performed by a single gynecologist who was aware of the TVS and TRS results but unaware of the MRI results. The pathologist was unaware of clinical and imaging findings.	**TRS** Sensitivity: 80.5% Specificity: 18.6% **MRI** Sensitivity: 90.4% Specificity: 66.1% **Uterosacral ligaments (n=317)** **TVS** Sensitivity: 70.86% Specificity: 92.77 **TRS** Sensitivity: 82.78% Specificity: 89.76% Both p<0.001 vs TVS and MRI **MRI** Sensitivity: 63.58% Specificity: 93.98% **Retrocervical (n=317)** **TVS** Sensitivity: 52.83% Specificity: 94.62% **TRS** Sensitivity: 50% Specificity: 96.06% **MRI** Sensitivity: 65.79% Specificity: 96.42% **Rectovaginal septum (n=317)** **TVS** Sensitivity: 86.36% Specificity: 94.87% **TRS** Sensitivity: 84.09% Specificity: 93.77% **MRI** Sensitivity: 72.73% Specificity: 95.24% **Rectal wall (n=317)** **TVS** Sensitivity: 88.46% Specificity: 98.87% **TRS** Sensitivity: 86.54%	of DIE especially in rectovaginal and ureter locations. But TVS and TRS both had high diagnostic accuracy for DIE indicating them as appropriate modalities of choice. Taking into account the fact that TRS could be performed in virgin individuals where TVS is not applicable, TRS remains an important noninvasive modality for diagnosis of DIE. Accordingly, MRI could be considered as the modality of choice for preoperative diagnosis and planning of patient with DIE. All these 3 modalities are experience dependent and their interpretation depends on the interpreter.	Flow and Timing: **Unclear** Potential applicability/ directness issues: **Not all cases undergo surgery; single centre.** Overall risk of bias: **High**

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 9)
				Specificity: 97.74% **MRI** Sensitivity: 76.92% Specificity: 96.6% **Ovarian fossa (n=317)** **TVS** Sensitivity: 62.71% Specificity: 95.74% **TRS** Sensitivity: 64.41% Specificity: 93.41% **MRI** Sensitivity: 66.1% Specificity: 98.06% **Bladder (n=317)** **TVS** Sensitivity: 100% Specificity: 99.68% **TRS** Sensitivity: 100% Specificity: 99.68% **MRI** Sensitivity: 100% Specificity: 99.68% **Ureter (n=317)** **TVS** Sensitivity: 100% Specificity: 100% **TRS** Sensitivity: 100% Specificity: 100% **MRI** Sensitivity: 100% Specificity: 100%		
Full citation Reid S, Espada M, Lu C, Condous G. To determine the optimal ultrasonographic screening method for rectal/rectosigmoid deep endometriosis: Ultrasound "sliding sign," transvaginal ultrasound direct	**Population** Consecutive women with suspected endometriosis **Sample size** 410 included, **376** with complete TVS and laparoscopic outcomes available. 20.2% had rectal or rectosigmoid DIE at surgery,	Index test 2D-TVS (no BP reported) Reference standard Laparoscopic visualisation with histological examination	All women underwent detailed TVS using a 7.5 MHz transvaginal probe (LOGIQ-e -I, General Electric, or Medison X8, V20, or XG, Samsung Medison) prior to laparoscopy. All TVS examinations were completed by one of two operators, both of whom were experienced in performing gynecological TVS scans for the prediction of pelvic DIE. The 5-domain	****2x2 in text**** **Rectal/ rectosigmoid DIE (n=376)** **TVS "sliding sign"** Sensitivity: 73.7% (95% CI 62.3, 83.1) Specificity: 90.3% (86.4, 96.4) **TVS "direct visualisation"**	Direct visualisation of rectal/ rectosigmoid DIE with TVS gave the highest accuracy (91.2%) and sensitivity (86.8%), and the combination of direct visualisation and a negative "sliding sign" gave the highest specificity (95.3%) and PPV (79.1%), for the prediction of rectal/ rectosigmoid DIE at laparoscopy.	Patient selection: **High** Index Test: **Low** Reference Standard: **High** Flow and Timing: **Unclear**

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 9)
visualization or both?. Acta Obstet Gynecol Scand. 2018. 97:1287-1292. **Country** Australia **Aim** To evaluate the TVS "sliding sign" alone, direct visualisation of the bowel with TVS, and the combination of both methods, to determine the optimal TVS method for the prediction of rectal/ rectosigmoid DIE. **Study type** Prospective **Study dates** Jan 2009 to Feb 2017 **Source of funding** The authors declared no COIs.	of which 79% had complete surgical excision and histology. **Setting** Tertiary referral pelvic pain clinics at two centres **Subgroup analysis** None **Inclusion criteria** Women presenting with symptoms of CPP and/or a history of endometriosis. **Exclusion criteria** None reported	<u>Prior tests</u> History and clinical examination	sonographically based approach was used (uterus, ovaries, POD status, anterior and posterior compartments for DIE in the bladder/ureters/uterovesical fold/rectum/rectosigmoid, RVS, uterosacral ligaments, and vagina). The laparoscopic surgeries were performed within 6 months of TVS by 13 different surgeons at nine different hospitals. Surgeons were not blinded to TVS findings. Rectal DIE was defined as the presence of DIE between the anal sphincter and the rectum at the level of the uterine fundus. Rectosigmoid DIE was defined as the presence of DIE at the level of the uterine fundus.	Sensitivity: 86.8% (77.1, 93.5) Specificity: 92.3% (88.7, 95.1) **TVS "combined approach"** Sensitivity: 69.7% (58.1, 79.8) Specificity: 95.3% (92.3, 97.4) **Rectosigmoid (n=376)** **TVS "sliding sign"** Sensitivity: 77.4% (58.9, 90.4) Specificity: 82.3% (77.9, 86.2) **TVS "direct visualisation"** Sensitivity: 71.0% (52, 85.8) Specificity: 96.2% (93.6, 98) **TVS "combined approach"** Sensitivity: 54.8% (36, 72.7) Specificity: 97.1% (94.7, 98.6) **Rectum (n=376)** **TVS "sliding sign"** Sensitivity: 72.4% (59.1, 83.3) Specificity: 86.5% (82.2, 90) **TVS "direct visualisation"** Sensitivity: 72.4% (59.1, 83.3) Specificity: 92.8% (89.3, 95.4) **TVS "combined approach"** Sensitivity: 58.6% (44.9, 71.4)	The TVS "sliding sign" alone does not perform as well as direct visualisation of rectal DIE (with or without the "sliding sign") for the prediction of rectal DIE preoperatively. A negative "sliding sign" should alert the sonographer to the increased risk of bowel DIE, and prompt a thorough assessment of the posterior compartment for sites of DIE. In expert hands, the "combined technique" …appears to provide the most accurate assessment for the identification of rectal DIE preoperatively, but a sequential study among patients with rectal/rectosigmoid visible nodules should be conducted to confirm this result. A limitation of the study is that those patients who were included in the study experienced CPP (hence, a high proportion of DIE would be expected in our study population) and therefore are a selected population. In addition, the sonologists did not perform the ultrasound techniques in isolation, and for example the presence of a negative "sliding sign" may have influenced the operator to assess the posterior compartment more thoroughly to seek out an underlying rectal DIE lesion.	Potential applicability/ directness issues: **Not all cases undergo surgery; referral centre more likely to see complex/ severe cases.** Overall risk of bias: **High**

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 9)
				Specificity: 95.3% (92.3, 97.3)		
Full citation Ferrero S, Biscaldi E, Vellone VG, Leone Robertu Maggiore U. Computed tomographic colonography vs rectal water contrast transvaginal sonography in diagnosis of rectosigmoid endometriosis: a pilot study. Ultrasound Obstet Gynecol. 2017. 49:515-523. **Country** Italy **Aim** To compare the performance of CTC and RWC-TVS in the diagnosis of rectosigmoid endometriosis. **Study type** Prospective **Study dates** Oct 2013 to Aug 2015 **Source of funding** Note reported.	**Population** Patients with clinical suspicion of rectosigmoid endometriosis **Sample size** 70 included. 57.1% had rectosigmoid endometriosis at surgery; 12.5% of patients with endometriosis had multifocal disease **Setting** Tertiary referral centre for the treatment of endometriosis **Subgroup analysis** Multifocal rectosigmoid endometriosis **Inclusion criteria** Patients of reproductive age scheduled for laparoscopy with strong suspicion of intestinal endometriosis based on symptoms and clinical examination. **Exclusion criteria** Previous surgical or radiological (MRI or double-contrast barium enema) diagnosis of intestinal endometriosis; history of colorectal surgery (except appendectomy); previous bilateral ovariectomy; contraindications to bowel preparation or CTC (such as non-compliant patients and rectal malformations) or a psychiatric disorder.	Index test 1 RWC-TVS with simple BP Index test 2 CTC with BP (no iodinated contrast) Reference standard Laparoscopy with histological examination Prior tests Symptoms and clinical examination	Different investigators performed RWC-TVS and CTC independently and blindly. All patients had RWC-TVS then CTC. RWC-TVS was performed by a sonographer with extensive experience in the diagnosis of intestinal endometriosis, using a Voluson E6 machine with a transvaginal transducer (GE Medical Systems). Patients had a rectal enema a few hours before. Water distension of the rectum was used after standard TVS. CTC was performed by a radiologist with more than 5 years' experience in virtual colonoscopy scans and in the diagnosis of intestinal endometriosis, using a 16-section multidetector CT scanner (LightSpeed 16; GE Medical Systems) with patients in the supine and prone positions. Efforts were made to decrease the CT radiation dose; an ASIR technique was used. 3D images were used in cases of problem solving; diagnosis was based on 2D images and MPR. Extracolonic assessment was based on 2D MPR. Rectovaginal septum and extrinsic bowel wall impressions were assessed with 3D transparent view reconstruction. Before CTC, patients followed a low-residue diet for 3 days. On the day before CTC, patients had a liquid diet, an intestinal preparation and fecal tagging. A standardised examination protocol was used. A 12-Fr Foley catheter was introduced by the radiologist into the distal rectum before the scan and the colon was manually dilated with room air.	****No 2x2 data**** **Rectosigmoid endometriosis (n=70)** **RWC-TVS** Sensitivity: 92.5% (78.6, 98.4) Specificity: 96.7% (82.9, 99.9) **CTC** Sensitivity: 92.5% (79.6, 98.4) Specificity: 86.7% (69.3, 96.2) **Multifocal rectosigmoid endometriosis (n=70)** **RWC-TVS** Sensitivity: 80.0% (28.4, 99.5) Specificity: 97.1% (85.1, 99.9) **CTC** Sensitivity: 40.0% (5.3, 85.3) Specificity: 91.4% (76.9, 98.2)	This study shows that RWC-TVS and CTC have similar accuracy in the diagnosis of rectosigmoid endometriosis. Patients tolerate better RWC-TVS than CTC; however, CTC is more precise than RWC-TVS in estimating the distance between endometriotic bowel nodules and the anus. Future studies should assess the role of CTC in diagnosing whole colon endometriotic lesions in patients with rectosigmoid endometriosis diagnosed by TVS. If CTC is shown to be accurate in this diagnosis, it may be combined with TVS to achieve a complete preoperative assessment of the bowel in order to offer patients adequate counseling and the most appropriate one-step surgical treatment. A limitation of this research is that, during the study period, rectosigmoid endometriosis was treated surgically only by segmental bowel resection. Therefore, it was not possible to estimate whether the preoperative workup might influence the type of surgery performed. Although TVS should be considered the first-line investigation for the diagnosis of rectosigmoid endometriosis, CTC may be considered in settings in which sonographers experienced in the diagnosis of endometriosis are not available. An advantage of CTC compared with RWC-TVS is that it may enable other indirect signs of intestinal pathologies to be identified (lymphadenopathies, ascites and	Patient selection: **High** Index Test: **Low** Reference Standard: **High** Flow and Timing: **Low** Potential applicability/ directness issues: **Not all cases undergo surgery; referral centre more likely to see complex/ severe cases; single centre. Unclear if CTC protocol is standard.** Overall risk of bias: **High and small sample size**

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 9)
			Interval between RWC-TVS and CTC was 1–3 weeks. Interval between CTC and laparoscopic surgery was 1-3 months. CTC and RWC-TVS results were compared with surgical and histological findings. Surgeons were not blinded to imaging results.		calcifications), which in some cases may cause symptoms mimicking intestinal endometriosis. The most relevant disadvantage of CTC is the exposure to X-rays; however, a low-dose CTC protocol was used.	
Full citation Jiang J, Liu Y, Wang K, Wu X, Tang Y. Rectal water contrast transvaginal ultrasound versus double-contrast barium enema in the diagnosis of bowel endometriosis. BMJ Open. 2017. 7:e017216. **Country** China **Aim** To compare the accuracy between RWC-TVS and double-contrast barium enema (DCBE) in evaluating the bowel endometriosis presence as well as its extent. **Study type** Prospective **Study dates** May 2012 to Aug 2016 **Source of funding** The authors declared no COIs.	**Population** Patients with clinical suspicion of bowel endometriosis **Sample size** 198 included. 55.6% had bowel endometriosis nodules; 14.1% had infiltration of intestinal serosa; 41.4% had pelvic endometriosis without intestinal lesions. **Setting** Department Ultrasound, Tianjin First Center Hospital. **Subgroup analysis** None **Inclusion criteria** Reproductive age scheduled for laparoscopy with suspicion of deep pelvic endometriosis based on gastrointestinal symptoms and clinical examination; desire for complete surgical endometriosis excision. **Exclusion criteria** Precedent bilateral ovariectomy; radiological diagnosis of bowel endometriosis; examination of barium radiology; colorectal surgery; hepatic or renal failure; suggestive intolerance for iodinated contrast medium; refusal of DCBE; psychiatric disorders.	Index test 1 RWC-TVS Index test 2 DCBE with BP Reference standard Laparoscopy with histological examination Prior tests Symptoms and clinical examination	RWC-TVS was conducted using a Voluson E6 machine connected with a transvaginal transducer. A flexible catheter was inserted into the rectum lumen and warm saline was injected into the rectum and sigmoid. Two physicians performed RWC-TVS using a standardised procedure. Al DCBE procedures were conducted by a motorised and tilting table to perform radiological and fluoroscopic examination. Before DCBE, patients followed a low-residue diet for 1 day. Examination was conducted after intramuscular administration of scopolamine to induce colonic hypotonia. Radiologist conducting DCBE and gynaecologists conducting TVS were blinded to clinical data and imaging but knew that intestinal endometriosis was suspected. The results of DCBE and RWC-TVS were compared with surgical and pathologic findings. The surgical team comprised colorectal and gynaecological surgeons with experience in bowel endometriosis and pelvic treatment. Surgeons carefully examined the results and images by DCBE and RWC-TVS prior to laparoscopy, which was performed systematically. Surgery was performed within 1 month of imaging.	****2x2 in text**** **Bowel and rectosigmoid endometriosis (n=198)** **RWC-TVS** Sensitivity: 88.2% Specificity: 97.3% **DCBE** Sensitivity: 96.4% Specificity: 100% No significant difference in accuracy	This study demonstrated RWC-TVS as a very reliable technique to determine the bowel endometriosis presence and extent and it has similar accuracy to that of DCBE. Nevertheless, RWC-TVS may underestimate multiple bowel nodule presence sometimes and be conducted easily in the ambulatory setting; also, it is easily tolerated by the patients. It is hypothesised to combine DCBE and TVS to attain a complete bowel preoperative assessment so as to provide adequate counselling to the patients and the most suitable surgical treatment in one step. The current study has several limitations. First, experience of ultrasonographer conducting RWC-TVS may affect the accuracy of the techniques in bowel endometriosis diagnosis. Second, the surgeons know the findings by RWC-TVS and DCBE… Third, DCBE and RWC-TVS did not estimate the circumference percentage of intestinal wall that was infiltrated by the endometriosis, a criterion for choosing between bowel resection and nodulectomy…At last, the study was also limited in that we didn't assess the accuracy of the two techniques in estimating the distance between the lower margin of the lesion and the anal verge, which should be addressed in our follow-up study.	Patient selection: **High** Index Test: **Low** Reference Standard: **High** Flow and Timing: **Low** Potential applicability/ directness issues: **Not all cases undergo surgery** Overall risk of bias: **High**

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 9)
Full citation Leone Roberti Maggiore U, Biscaldi E, Vellone VG, Venturini PL, Ferrero S. Magnetic resonance enema vs rectal water-contrast transvaginal sonography in diagnosis of rectosigmoid endometriosis. Ultrasound Obstet Gynecol. 2017. 49:524-532. **Country** Italy **Aim** To compare the accuracy of magnetic resonance enema (MR-e) and RWC-TVS in the diagnosis of rectosigmoid endometriosis. **Study type** Prospective **Study dates** Nov 2008 to Dec 2013 **Source of funding** Not reported.	**Population** Consecutive patients referred for clinical suspicion of rectosigmoid endometriosis **Sample size** 286 who underwent both diagnostic examination and surgery. 52.8% had rectosigmoid endometriosis; 8.6% had infiltration of the mucosa **Setting** Tertiary centre with expertise in endometriosis **Subgroup analysis** None **Inclusion criteria** Reproductive age; suspicion of deep pelvic endometriosis on the basis of gynecological symptoms and vaginal examination and/or presence of gastrointestinal symptoms. **Exclusion criteria** Previous bilateral ovariectomy, previous examinations diagnosing bowel endometriosis (e.g. double-contrast barium enema, multidetector CT enema or rectal endoscopic sonography), previous bowel surgery; renal or hepatic failure; contraindications to MR.	Index test 1 RWC-TVS with simple BP Index test 2 Magnetic resonance enema (MR-e) Reference standard Laparoscopic surgery with histological confirmation Prior tests Symptoms with or without vaginal examination	Two physicians performed RWC-TVS and MR-e independently. They knew the clinical data and that rectosigmoid endometriosis was suspected; however, each was blinded to the findings of the other imaging technique. RWC-TVS was performed using a standardised protocol using a Voluson E6 ultrasound machine (GE Medical Systems). A few hours before TVS, a rectal enema was used. After the transducer was introduced into the vagina, a 6 mm flexible catheter was inserted through the anal os into the rectal lumen and warm sterile saline solution was injected into the rectosigmoid under sonographic guidance. MR-e was performed on a 1.5-T magnet (Signa Excite HDx, GE Medical Systems) using an 8-channel phased-array coil, following a standardised protocol. Retrograde distension was performed initially in the left lateral decubitus, then in the horizontal position to reduce abdominal wall movements and respiratory artifacts. Sonographic gel was introduced using a syringe connected to a 20-Fr Foley catheter to distend the rectum and the sigmoid colon. Intestinal hypotonisation was not used. Laparoscopic surgery was performed within 3 months by unblinded surgeons.	****No 2x2 data**** **Presence of rectosigmoid endometriosis** **RWC-TVS (n=286)** Sensitivity: 92.7% (87.3, 96.3) Specificity: 97.0% (92.6, 99.2) **MR-e (n=286)** Sensitivity: 95.4% (90.7, 99.1) Specificity: 97.8% (93.6, 99.5) **Infiltration of mucosal layer of bowel wall** **RWC-TVS (n=286)** Sensitivity: 76.9% (46.2, 95.0) Specificity: 86.1% (81.4, 90.0) **MR-e (n=286)** Sensitivity: 66.7% (34.9, 90.1) Specificity: 85.0% (80.3, 89.0)	This study shows that RWC-TVS and MR-e have similar accuracy in the diagnosis of rectosigmoid endometriosis. The mean intensity of pain perceived during RWC-TVS and MR-e is similar but severe pain is perceived by the patients more frequently during MR-e. However, the methodology of the two imaging techniques was different (in terms of type of catheters used and volume of fluid instilled) and this may have influenced the discomfort perceived by the patients. RWC-TVS should be the first-line investigation in patients with clinical suspicion of rectosigmoid endometriosis and physicians should be trained in performing this examination. Considering that MR-e is more expensive than RWC-TVS, it should be used only when the findings of RWC-TVS are unclear.	Patient selection: **Low** Index Test: **Low** Reference Standard: **High** Flow and Timing: **Low** Potential applicability/ directness issues: **Not all cases undergo surgery; referral centre more likely to see complex/ severe cases; single centre.** Overall risk of bias: **High**
Full citation Ros C, Martínez-Serrano MJ, Rius M, Abrao MS, Munrós J, Martínez-Zamora MÁ, Gracia M, Carmona F. Bowel preparation improves the accuracy of transvaginal ultrasound in the diagnosis of rectosigmoid deep	**Population** Consecutive patients referred for suspicion of DIE **Sample size** 185 consecutive patients, **40** underwent both diagnostic examination and surgery. 40% had a history of surgery for endometriosis	Index test 1 TVS without BP Index test 2 TVS with BP Reference standard Laparoscopic surgery with	All participants underwent 2 TVS examinations within an interval of 2 weeks to 3 months. The first TVS was performed without BP, whereas the second procedure was performed after a 3-day low-residue diet and 2 enemas. All TVS studies were performed by the same trained gynecologist who was blinded to the	****2x2 available**** **Presence of rectosigmoid nodules** **TVS without BP (n=40)** Sensitivity: 73% Specificity: 88% **TVS with BP (n=40)**	The use of TVUS with BP allows and facilitates the detection of more rectal nodules of DIE in patients with suspected endometriosis, suggesting the need to include BP in TVUS procedures in order to improve the accuracy of the diagnosis of DIE with rectosigmoid involvement. Other prospective	Patient selection: **Unclear** Index Test: **Low** Reference Standard: **High and small sample size**

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 9)
infiltrating endometriosis: a prospective study. Journal of minimally invasive gynecology. 2017. 24:1145-51. **Country** Spain **Aim** To compare the accuracy of TVUS with and without bowel preparation to detect and describe intestinal nodules of DIE with laparoscopic findings. **Study type** Prospective **Study dates** Nov 2014 to May 2015 **Source of funding** The authors declared no COIs.	37.5% had rectosigmoid involvement on surgery **Setting** Tertiary university hospital **Subgroup analysis** None **Inclusion criteria** Suspicion of DIE based on pain symptoms and/or physical examination; met surgical criteria: pelvic pain unresponsive to medical treatment, a hydrosalpinx in infertile patients, ovarian endometriosis cysts >7 cm in size, and rectosigmoid and/or ureteral stenosis. **Exclusion criteria** Virgins; patients in whom TVUS was not possible.	histological confirmation Prior tests Symptoms and/or physical examination	clinical data and the results of the first TVS during the second examination with BP. TVS was performed according to a standard method using a microconvex endocavity probe (type RIC5-9, Voluson-V730 Expert; GE). The probe was introduced transvaginally, and the anterior rectal wall, rectosigmoid junction, and lower sigmoid colon were examined as far as possible. No other solution or transrectal gel was used. Bowel involvement was suspected when a long, nodular, hypoechogenic lesion adhering to the anterior wall of the rectum was observed. Rectosigmoid DIE was considered when the lesions affected at least the muscularis propria layer. The surgical interventions were performed by expert endometriotic surgeons. Histologic evaluation was performed by a single pathologist.	Sensitivity: 100% Specificity: 96%	studies including patients with endometriosis, independent of the surgical approach, are needed. With regard to the limitations of the present study, the aim of the present study was to evaluate the usefulness of BP in the detection of rectosigmoid DIE nodules. However, we did not assess whether this method also increases the detection of DIE affecting the anterior compartment, uterosacral ligaments, the vagina wall, or the rectovaginal septum. Lastly, the sample included patients with surgical criteria, and, considering that this disease is currently being managed medically and surgery can be avoided or delayed in a growing proportion of cases, the results cannot be extrapolated to the population without surgical endometriosis.	Flow and Timing: **Low** Potential applicability/ directness issues: **Not all cases undergo surgery; unclear if BP protocol is standard.** Overall risk of bias: **High and small sample size**
Full citation Young SW, Dahiya N, Patel MD, Abrao MS, Magrina JF, Temkit MH, Kho RM. Initial accuracy of and learning curve for transvaginal ultrasound with bowel preparation for deep endometriosis in a US tertiary care center. Journal of minimally invasive gynecology. 2017. 24:1170-6. **Country** United States **Aim** To evaluate the diagnostic accuracy of TVUS-BP after a short training period and to determine the number of cases required to achieve proficiency. The secondary	**Population** Consecutive patients who underwent a dedicated TVS-BP for suspicion of deep endometriosis based on symptoms and/or physical examination **Sample size** 117 consecutive patients, 57 who underwent both complete diagnostic examination and surgery. 40.4% had deep endometriosis **Setting** Tertiary referral center **Subgroup analysis** None **Inclusion criteria** Referred for TVS with BP; presented with noncyclic	Index test 3D-TVS with BP Reference standard Laparoscopic surgery with histological confirmation (within 1-year) Prior tests Symptoms and/or physical examination	Included patients who underwent a dedicated TVUS-BP for DE, identified using an electronic medical record search engine. All TVS examinations were performed with a Siemens S2000 ultrasound unit (Siemens Medical Solutions) by a single radiologist with 1 year of dedicated fellowship training. Transvaginal imaging was performed with a 9-MHz transvaginal transducer (Siemens 9EVF4) with 3D and steering capabilities. Patients took a laxative the day before the examination and a rectal Fleet enema 1 hour before the study. The complete TVUS-BP scanning protocol included a renal scan, standard AIUM views of the pelvis, and an extended evaluation of specific areas in the pelvis with demonstration of mobility of organs.	**** 2x2 in text**** **Rectosigmoid and/or rectovaginal septum DIE** **TVS with BP (n=57)** Sensitivity: 94% (70,100) Specificity: 100% (91,100) **Retrocervical and/or uterosacral ligament DIE** **TVS with BP (n=57)** Sensitivity: 86% (65, 97) Specificity: 94% (81, 99)	A newly applied TVUS-BP protocol for detection of pelvic deep endometriosis is highly accurate and required only a modest learning curve to achieve procedural proficiency in a US tertiary referral center where physicians interpret but typically do not perform TVUS exams. Overcoming diagnostic uncertainty regarding minimal or equivocal disease appeared to be an important factor in the initial learning curve. With adequate training, TVUS-BP may be adapted as a primary diagnostic tool for detecting pelvic deep endometriosis.	Patient selection: **Unclear** Index Test: **Low** Reference Standard: **High** Flow and Timing: **Unclear** Potential applicability/ directness issues: **Not all cases undergo surgery.** Overall risk of bias: **High and small sample size**

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 9)
purpose was to determine whether disease severity, as judged by ultrasound findings, influence the duration of examination and the learning curve. **Study type** Retrospective **Study dates** May 2012 to June 2015 **Source of funding** The authors declared no COIs.	pelvic pain of at least 6 months' duration, and/or physical examination findings concerning for deep endometriosis. **Exclusion criteria** Age <18 years; those with previous imaging (such as MRI) confirming deep endometriosis; inadequate BP; non-compliance with scanning.		Findings from surgery were abstracted from the operative report and correlated with the ultrasound findings.			
Full citation Baggio et al. 2016 **Country** Italy **Study type** Prospective *See Table 6*	**Population** Patients suspected of DIE enrolled to undergo surgical treatment **Sample size** 92 patients for TVS. *See Table 6*	Index test 1 CA 125 >35 µg/mL Index test 2 2D-TVS[22] (without BP) Index test 3 CTC with BP and iodinated contrast Index test 4 Intestinal symptoms Reference standard Laparoscopic findings and subsequent pathological confirmation	TVS scans were carried out always by the same two examiners who were blinded to patients' clinical data. They had more than 15 years of experience as advance obstetrics sonographers but only a basic formation in gynecologic sonography. The scanner was a GE Healthcare Voluson E8 Expert with a wide band endocavity Micro-convex Array Transducer (2D) in association with an Abdominal Real-time 4D Wide Band Convex Transducer when important colonic segments were not correctly visualised. Each examination was interpreted in real time and documented in printed photographs. TVS protocol included, in addition to routine analysis of the uterus and ovaries, the study of the bowel segments (in particular rectum, sigmoid colon, and cecum). Sonographically, DIE involvement of the bowel was suspected in the presence of solid, focal, tubular, and hypoechogenic bowel lesions with slightly irregular margins and in most cases with a thinner section or a "tail" at one end, resembling a comet.	****2x2 available but inconsistently reported in publication for TVS**** **TVS** Sensitivity: 0.41 Specificity: 0.93 *See Table 6 for other tests*	*See Table 6*	Overall risk of bias assessment: **High and small sample size** *See Table 6*

[22] 4D transabdominal was used in some cases (data not shown separately).

Abbreviations: AIUM, American Institute of Ultrasound in Medicine; ASIR, adaptive statistical iterative reconstruction; BP, bowel preparation; COI, conflict of interest; CPP, chronic pelvic pain; CTC, computed tomography colonography; DIE, deep infiltrating endometriosis; MPR, multiplanar reconstruction; NN, not a number; NS, not significant; POD, Pouch of Douglas; TVS, transvaginal sonography.

Table 9 QUADAS-2 Diagnostic accuracy checklist: Diagnosis of endometriosis – transvaginal ultrasound

Domain	Question	Ferrero 2019a	Ferrero 2019b	Rosefort 2019	Alborzi 2018	Reid 2018	Ferrero 2017	Jiang 2017	Leone Roberti Maggiore 2017	Ros 2017	Young 2017
Patient selection											
Signalling questions	Was a consecutive or random sample of patients enrolled?	Yes	Unclear (not reported)	Yes (probably consecutive)	Yes	Yes	Unclear (probably not)	Unclear (probably not)	Yes	Yes	Yes
	Was a case-control design avoided?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Did the study avoid inappropriate exclusions?	Yes	Yes (although 3 lost to FU)	No (large myomas an exclusion)	Yes	Unclear (no exclusion criteria)	Yes	Yes	Yes	Yes	Unclear (excluded inadequate BP)
Risk of Bias	**Could the selection of patients have introduced bias?**	**Low**	**Unclear**	**High**	**Low**	**Unclear**	**High**	**High**	**Low**	**Low**	**Unclear**
Concerns regarding applicability	Are there concerns that the included patients and setting do not match the review question?	High (referral centre more likely to see complex/ severe cases; single centre)	High (referral centre more likely to see complex/ severe cases; single centre)	High (single centre)	High (single centre)	High (referral centre for CPP more likely to see severe cases)	High (referral centre more likely to see complex/ severe cases; single centre)	Unclear (China)	High (referral centre more likely to see complex/ severe cases; single centre)	Unclear	Unclear
Index Test											
Signalling questions	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	If a threshold was used, was it pre-specified?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Risk of bias	**Could the conduct or interpretation of the index test have introduced bias?**	**Low**	**Low**	**High (some people had multiple TVUS)**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**

Domain	Question	Ferrero 2019a	Ferrero 2019b	Rosefort 2019	Alborzi 2018	Reid 2018	Ferrero 2017	Jiang 2017	Leone Roberti Maggiore 2017	Ros 2017	Young 2017
Concerns regarding applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High (BP protocol more extensive than in practice)	Unclear (if BP protocol is standard)	Unclear (limited details provided; different operators untrained in DIE)	Low	Low	Unclear (if CTC protocol is standard)	Unclear	Low	Unclear (if BP protocol is standard)	Low
Reference Standard											
Signalling questions	Is the reference standard likely to correctly classify the target condition?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Were the reference standard results interpreted without knowledge of the results of the index tests?	No (surgeons aware of imaging findings; unclear if histologists blinded)	No (surgeons aware of imaging findings; unclear if histologists blinded)	No (surgeons aware of imaging findings; unclear if histologists blinded)	No (surgeons aware of TVS/TRS findings but histologists blinded)	No (surgeons aware of imaging findings; unclear if histologists blinded)	No (surgeons aware of imaging findings; unclear if histologists blinded)	No (surgeons aware of imaging findings; unclear if histologists blinded)	No (surgeons aware of imaging findings; unclear if histologists blinded)	No (C)	No (not stated but unlikely)
Risk of Bias	**Could the reference standard, its conduct, or its interpretation have introduced bias?**	**High**	**High**	**High**	**High**	**High**	**High**	**High**	**High**	**High**	**High**
Concerns regarding applicability	Are there concerns that the target condition as defined by the reference standard does not match the question?	High (not all patients will undergo surgery)	High (not all patients will undergo surgery)	High (not all patients will undergo surgery)	High (not all patients will undergo surgery)	High (not all patients will undergo surgery)	High (not all patients will undergo surgery)	High (not all patients will undergo surgery)	High (not all patients will undergo surgery)	High (not all patients will undergo surgery)	High (not all patients will undergo surgery)
Flow and Timing											
Signalling questions	Was there an appropriate interval between index test and reference standard?	Yes (mean 16.2 weeks between TVS+BP and surgery)	Yes (mean 15.6 weeks between TVS+BP and surgery)	Unclear (interval not reported)	Unclear (interval not reported)	Unclear (within 6 months)	Yes (1-3 months)	Yes (1 month)	Yes (within 3 months)	Yes (3.6±1.5 months)	Unclear (up to 1 year)

Domain	Question	Ferrero 2019a	Ferrero 2019b	Rosefort 2019	Alborzi 2018	Reid 2018	Ferrero 2017	Jiang 2017	Leone Roberti Maggiore 2017	Ros 2017	Young 2017
	Did all patients receive a reference standard?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Did all patients receive the same reference standard?	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
	Were all patients included in the analysis?	Yes	Yes	Unclear (some participants had 2 TVS)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Risk of Bias	**Could the patient flow have introduced bias?**	**Low**	**Low**	**Unclear**	**Unclear**	**Unclear**	**Low**	**Low**	**Low**	**Low**	**Unclear**

Abbreviations: BP, bowel preparation; CPP, chronic pelvic pain; CTC, computed tomographic colonography; DIE, deep infiltrating endometriosis; FU, follow up; N/A, not applicable; TRS, transrectal sonography; TVS, transvaginal ultrasound.

Note: Risk of Bias assessments for Berger et al. 2019; Chen et al. 2019; Baggio et al. 2016 are located in Table 7.

Transvaginal plus transabdominal ultrasound

Table 10 Evidence Summary: Diagnosis of endometriosis – transvaginal plus transabdominal ultrasound

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 11)
Full citation Hernandez Gutierrez A, Spagnolo E, Hidalgo P, Lopez A, Zapardiel I, Rodriguez R. Magnetic resonance imaging versus transvaginal ultrasound for complete survey of the pelvic compartments among patients with deep infiltrating endometriosis. Int J Gynecol Obstet. 2019. 146:390-395. **Country** Spain **Aim** To compare the performance of MRI and TVUS in detecting DIE, using Enzian classification. **Study type** Retrospective **Study dates** 01 Apr 2012 to 31 Dec 2014 **Source of funding** The authors declared no COIs.	**Population** Patients who presented with clinical suspicion of DIE **Sample size** 69 eligible presented, **48** fulfilled inclusion criteria. 100% had DIE **Setting** Endometriosis Unit of a university hospital **Subgroup analysis** Location of DIE **Inclusion criteria** Clinical objectivity at gynecologic examination; indication to undergo TVUS and MRI and finally surgical treatment. **Exclusion criteria** Previous hysterectomy, bowel resection, or urinary tract surgery (partial cystectomy or ureter reimplantation).	Index test 1 2D-TVUS plus transabdominal ultrasound with BP Index test 2 MRI with BP Reference standard Laparoscopic surgery with histological confirmation Prior tests Gynaecologic examination	TVUS was performed by a gynecologist who was an expert in gynecological ultrasound, using GE Voluson ultrasound machines (730 Pro and E6; GE Healthcare), equipped with 4–8 MHz abdominal probes and a transvaginal 5–9 MHz probe. The standardised protocol included bowel preparation with a simple rectal enema 12 hours prior to examination. Transabdominal scan with panoramic view of the pelvic organs and abdomen was systematically performed. This was followed by vaginal ultrasound examination. MRI was performed by a radiologist skilled in abdominal and pelvic radiology for endometriosis, who was blinded to the ultrasound results, using a 1.5T MRI device (GE Signa Explorer; GE Healthcare). Bowel preparation before MRI involved one dose of Puntualex with abundant hydration every 8 hours, 3 days prior to the procedure. Sonographic gel was introduced into the vagina and to distend the rectum and sigmoid colon. Enzian classification was used to report localisation of DIE using MRI or TVUS. Patients had a maximum interval of 2 months between imaging (MRI and TVUS) and laparoscopic surgery.	****No 2x2 data**** **Rectovaginal space (n=48)** **TVUS** Sensitivity: 65% Specificity: 88% **MRI** Sensitivity: 74% Specificity: 64% **Vagina (n=48)** **TVUS** Sensitivity: 67% Specificity: 96% **MRI** Sensitivity: 33% Specificity: 93% **Utero-sacral ligaments (n=48)** **TVUS** Sensitivity: 59% Specificity: 43% **MRI** Sensitivity: 67% Specificity: 43% **Rectosigmoid (n=48)** **TVUS** Sensitivity: 81% Specificity: 62% **MRI** Sensitivity: 69% Specificity: 87% **Bladder (n=48)** **TVUS** Sensitivity: 50% Specificity: 98% **MRI** Sensitivity: 67% Specificity: 100% **Ureter (n=48)** **TVUS** Sensitivity: 50%	TVUS provided a more accurate localisation of vaginal and rectovaginal endometriosis as compared with MRI; however, MRI should be recommended if a suspicion of bladder endometriosis exists. TVUS and MRI showed the same accuracy for detection of rectosigmoid endometriosis. The nodule size did not seem to influence the accuracy of the two techniques. The authors of the present study suggest that MRI is the gold standard in the management of women who complain of dysuria, bladder pain, urgency, and less often hematuria with a gynecologic examination and ultrasound findings suspicious for bladder endometriosis. Another strength of the present study was the use of Enzian classification of DIE, as this provided adequate mapping of deep endometriosis localisations and enabled radiologists, sonographers and gynecologic surgeons to easily share the diagnostic findings. Another limitation of the study could be the high prevalence of DIE in the data (100% of patients included in the study) which could influence the sensitivity and specificity of the imaging techniques: this is because the study was conducted in an endometriosis referral center.	Patient selection: **Unclear** Index Test: **Low** Reference Standard: **Unclear** Flow and Timing: **Unclear** Potential applicability/ directness issues: **Not all patients with DIE undergo surgery; referral centre therefore more likely to see complex/ severe cases; single centre.** **Unclear if transabdominal and transvaginal scan is standard practice.** Overall risk of bias: **High and small sample size**

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 11)
				Specificity: 95% **MRI** Sensitivity: 33% Specificity: 98%		
Full citation Zannoni L, Del Forno S, Coppola F, Papadopoulos D, Valerio D, Golfieri R, Caprara G, Paradisi R, Seracchioli R. Comparison of transvaginal sonography and computed tomography–colonography with contrast media and urographic phase for diagnosing deep infiltrating endometriosis of the posterior compartment of the pelvis: a pilot study. Japanese journal of radiology. 2017. 35:546-54. **Country** Italy **Aim** To compare the diagnostic accuracy of TVS and CTCU in the preoperative detection of DIE. **Study type** Prospective **Study dates** May 2011 to May 2013 **Source of funding** The authors declared no COIs.	**Population** Patients with clinical suspicion of DIE **Sample size** 103 eligible patients, 47 who underwent both complete diagnostic examination and surgery. 95.7% had at least one DIE nodule in posterior compartment; 4.3% had superficial and ovarian endometriosis **Setting** Tertiary center for the diagnosis and treatment of endometriosis **Subgroup analysis** Location of DIE **Inclusion criteria** Suspicion of posterior DIE; pain score; clinical objectivity at gynaecological examination; childbearing age; indication to undergo TVS and CTCU; intention to undergo surgical treatment. **Exclusion criteria** Previous surgery for endometriosis; previous radical surgery of the bowel or of the urinary tract; previous bilateral oophorectomy; previous radiological studies for the diagnosis of endometriosis of intestinal or urinary tract with eventual episodes of intolerance to iodinated	Index test 1 TVS without BP including transabdominal scan Index test 2 Computed tomography colonography with contrast media and urographic phase (CTCU) with mild BP Reference standard Laparoscopic surgery with histological confirmation (within 1-month) Prior tests Symptoms and gynaecological examination	TVS and CTCU were performed independently by different experienced operators who were only aware of the suspicion of posterior compartment endometriosis. TVS was performed by one gynaecologist with more than 5 years' experience in gynaecological ultrasound, using a device (GE Voluson S8 ultrasound system, GE Medical Systems) equipped with a transvaginal ultrasound probe 5.0–9.0 MHz. The variable of interest was the localisation of the nodules of pelvic DIE. Initially the uterus and ovaries were evaluated, then the posterior then anterior compartment. A transabdominal ultrasound scan to assess the seat of the kidneys and exclude the presence of hydroureteronephrosis was always performed. For CTCU a 64-row CT scanner (VCT Lightspeed 64, GE Healthcare) was used, following a standardised protocol. A 24 Foley rectal catheter was placed to achieve colonic distension by introducing air. Patients were scanned in the supine position through the diaphragm to the public symphysis, then in prone. Before CTCU, patients had a low fibre diet for 3 days and a laxative the day before. The results of TVS and CTCU were compared with histology. Surgical treatment was performed by a single experienced surgeon within 1 month from diagnostic tests.	****No 2x2 data**** **Presence of intestinal DIE** **TVS (n=47)** Sensitivity: 97.5% Specificity: 33.3% **CTCU (n=47)** Sensitivity: 78.0% Specificity: 50.0% **Presence of right ureteral DIE** **TVS (n=47)** Sensitivity: 10.0% Specificity: 94.8% **CTCU (n=47)** Sensitivity: 60.0% Specificity: 70.2% **Presence of left ureteral DIE** **TVS (n=47)** Sensitivity: 28.5% Specificity: 96.3% **CTCU (n=47)** Sensitivity: 57.1% Specificity: 76.9%	TVS should be regarded as an accurate, radiation-free first-line diagnostic modality for patients with suspicion of posterior endometriosis. CTCU should be regarded as a complementary imaging modality, particularly for sigmoid or ureteral endometriosis. The preoperative use of hormonal treatments that often determine atrophy in DIE nodules, making them less visible with the methods of study, was considered as a potential confounder. A problematic element of our study is the high prevalence of posterior DIE in the study population, but this is due to the fact that patients with particularly severe endometriosis are addressed to our centre. Furthermore, it is noteworthy that a role in favour of the diagnostic performance of TVS compared CTCU can be connected directly to the operators, because the sonographer, as well as gynaecologist, performs a dynamic and interactive examination to the patient, while the radiologist is more detached.	Patient selection: **Unclear** Index Test: **Low** Reference Standard: **Unclear** Flow and Timing: **Low** Potential applicability/ directness issues: **Not all patients with DIE undergo surgery; referral centre therefore more likely to see complex/ severe cases; single centre.** **Unclear if transabdominal and transvaginal scan is standard practice.** Overall risk of bias: **High and small sample size**

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 11)
	contrast; renal or hepatic failure.					

Abbreviations: BP, bowel preparation; COI, conflict of interest; CTCU, computed tomography colonography with contrast media and urographic phase; DIE, deep infiltrating endometriosis; MRI, magnetic resonance imaging; TVUS, transvaginal ultrasound.

Table 11 QUADAS-2 Diagnostic accuracy checklist: Diagnosis of endometriosis – transvaginal plus transabdominal ultrasound

Domain	Question	Hernandez Gutierrez 2019	Zannoni 2017
Patient selection			
Signalling questions	Was a consecutive or random sample of patients enrolled?	Unclear (not reported but probably was)	Unclear (not reported)
	Was a case-control design avoided?	Yes	Yes
	Did the study avoid inappropriate exclusions?	Yes (although 3 missing data)	Yes
Risk of Bias	**Could the selection of patients have introduced bias?**	**Unclear**	**Unclear**
Concerns regarding applicability	Are there concerns that the included patients and setting do not match the review question?	High (referral centre – more likely to see complex/ severe cases; single centre)	High (referral centre – more likely to see complex/ severe cases; single centre)
Index Test			
Signalling questions	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	Yes
	If a threshold was used, was it pre-specified?	N/A	N/A
Risk of bias	**Could the conduct or interpretation of the index test have introduced bias?**	**Low**	**Low**
Concerns regarding applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear (if transabdominal and transvaginal scan is standard)	Unclear (if transabdominal and transvaginal scan is standard)
Reference Standard			
Signalling questions	Is the reference standard likely to correctly classify the target condition?	Yes	Yes
	Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear	Unclear
Risk of Bias	**Could the reference standard, its conduct, or its interpretation have introduced bias?**	**Unclear**	**Unclear**
Concerns regarding applicability	Are there concerns that the target condition as defined by the reference standard does not match the question?	Moderate (not all patients with DIE undergo surgery)	Moderate (not all patients with DIE undergo surgery)
Flow and Timing			
Signalling questions	Was there an appropriate interval between index test and reference standard?	Yes (≤2 months between imaging and surgery)	Yes (within 1 month)
	Did all patients receive a reference standard?	Yes	Yes

Domain	Question	Hernandez Gutierrez 2019	Zannoni 2017
	Did all patients receive the same reference standard?	Unclear	Yes
	Were all patients included in the analysis?	Yes	Yes
Risk of Bias	**Could the patient flow have introduced bias?**	**Unclear**	**Low**

Abbreviations: DIE, deep infiltrating endometriosis; N/A, not applicable.

Rectal scanning

Table 12 Evidence Summary: Diagnosis of endometriosis – rectal scanning

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 13)
Full citation Chen et al. 2019 **Country** China *See Table 6*	**Population** Patients with suspected RVE **Sample size** 29 consecutive patients; 21 patients (72.4%) had RVE *See Table 6*	Index test 1 Physical examination Index test 2 TVS (without BP) Index test 3 Pelvic MRI with gadolinium-based contrast agent Index test 4 RES (with rectal lavage) Reference standard Surgical and histologic findings	RES was performed using a linear array echoendoscope (Pentax EG-3630UA; Pentax Corporation) with a 14.5-mm-diameter end and diasonography with a Japanese Hitachi EUB-6500 following a standardised protocol. The standard probe frequency used to detect RVE was 6 to 10 MHz. Patients were prepared with rectal lavage before RES. RES was performed by physicians experienced in endoscopic sonography in RES for diseases of female low genital tract.	****No 2x2 data**** **Diagnosis of RVE (n=21)** **RES** Sensitivity: 81.0% (57.4, 93.7) Specificity: 75.0% (35.6, 95.5) **Identification of rectal infiltration (n=15)** **RES** Sensitivity: 86.7% (58.4, 97.7) Specificity: 85.7% (56.2, 97.5) *See Table 6 for other tests*	*See Table 6*	Overall risk of bias assessment: **High and very small sample size** *See Table 6*
Full citation Alborzi et al. 2018 **Country** Iran *See Table 8*	**Population** Consecutive patients with signs and symptoms of endometriosis **Sample size** 317 enrolled 79.5% had DIE, 20.5% had no lesion. *See Table 8*	Index test 1 2D-TVS with BP Index test 2 TRS with BP Index test 3 MRI with contrast Reference standard Laparoscopy with histological examination Prior tests Clinical symptoms and physical examination	All TRS was performed using a 7.5 MHz linear probe (UltrasonixOP), 2 weeks after TVS, by a single gynaecologist blinded to clinical findings, following bowel prep. The examination protocol was similar to TVS and the same diagnostic criteria were applied.	****2x2 available**** **All DIE lesions (n=317)** **TRS** Sensitivity: 80.5% Specificity: 18.6% **Uterosacral ligaments (n=317)** **TRS** Sensitivity: 82.78% Specificity: 89.76% Both p<0.001 vs TVS and MRI **Rectal wall (n=317)** **TRS** Sensitivity: 86.54% Specificity: 97.74% *See Table 8 for other tests*	*See Table 8*	Overall risk of bias assessment: **High** *See Table 8*

Abbreviations: BP, bowel preparation; DIE, deep infiltrating endometriosis; MRI, magnetic resonance imaging; RES, rectal endoscopic sonography; RVE, rectovaginal endometriosis; TRS, transrectal ultrasonography; TVS, transvaginal sonography.

Table 13 QUADAS-2 Diagnostic accuracy checklist: Diagnosis of endometriosis – rectal scanning

Domain	Question	Chen 2019	Alborzi 2018
Patient selection			
Signalling questions	Was a consecutive or random sample of patients enrolled?	Yes	Yes
	Was a case-control design avoided?	Yes	Yes
	Did the study avoid inappropriate exclusions?	Unclear (not reported)	Yes
Risk of Bias	**Could the selection of patients have introduced bias?**	**Unclear**	**Low**
Concerns regarding applicability	Are there concerns that the included patients and setting do not match the review question?	High (tertiary referral centre – more likely to see complex/severe cases)	High (single centre)
Index Test			
Signalling questions	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	Yes
	If a threshold was used, was it pre-specified?	N/A	N/A
Risk of bias	**Could the conduct or interpretation of the index test have introduced bias?**	**Low**	**Low**
Concerns regarding applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear (physical examination (digital vaginal and rectovaginal examination); very experienced technicians/clinicians performing the tests	Low
Reference Standard			
Signalling questions	Is the reference standard likely to correctly classify the target condition?	Unclear (criteria for diagnosis not reported, however very experienced surgeons and pathologists)	Yes
	Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes	No (surgeons aware of TVS/TRS findings but histologists blinded)
Risk of Bias	**Could the reference standard, its conduct, or its interpretation have introduced bias?**	**Low**	**High**
Concerns regarding applicability	Are there concerns that the target condition as defined by the reference standard does not match the question?	High (only RVE not all patients with endometriosis undergo surgery)	High (not all patients will undergo surgery)
Flow and Timing			
Signalling questions	Was there an appropriate interval between index test and reference standard?	Unclear (interval not reported)	Unclear (interval not reported)
	Did all patients receive a reference standard?	Yes	Yes
	Did all patients receive the same reference standard?	No (all subjects underwent transvaginal surgery or laparotomy)	Yes
	Were all patients included in the analysis?	Yes	Yes
Risk of Bias	**Could the patient flow have introduced bias?**	**High**	**Unclear**

Abbreviations: N/A, not applicable; RVE, rectovaginal endometriosis; TRS, transrectal ultrasound; TVUS, transvaginal ultrasound.

Computed tomography

Table 14 Evidence Summary: Diagnosis of endometriosis – computed tomography

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 15)
Full citation Mehedintu C, Brînduse LA, Bratila E, Monroc M, Lemercier E, Suaud O, Collet-Savoye C, Roman H. Does computed tomography–based virtual colonoscopy improve the accuracy of preoperative assessment based on magnetic resonance imaging in women managed for colorectal endometriosis? J Minimally Invasive Gynecol. 2018. 25:1009-1017. **Country** France **Aim** To evaluate whether combining CT–based virtual colonoscopy (CTC) with MRI improves preoperative assessment of colorectal endometriosis. **Study type** Retrospective **Study dates** Jun 2015 to May 2016 **Source of funding** Grant from the "Carol Davila" University of Medicine and Pharmacy	**Population** Women with planned surgery for deep endometriosis infiltrating the rectum or sigmoid colon **Sample size** 71 patients underwent MRI followed by CTC for preoperative assessment. All were symptomatic and had relevant digestive discomfort. **Setting** University tertiary referral center **Subgroup analysis** None **Inclusion criteria** Women with planned surgery for DIE of the rectum or sigmoid colon; had preoperative assessment using MRI and CTC. **Exclusion criteria** Not reported.	Index test 1 1.5T MRI with ultrasonographic gel Index test 2 CTC with CO_2 distension and contrast Index test 3 MRI + CTC Reference standard Intraoperative findings (surgical and histological records) Prior tests Symptoms and clinical examination	Patients were referred for clinical and MRI examinations. MRIs performed outside the center were systematically reviewed by the center's expert radiologists. When clinical examination and/or MRI revealed colorectal DIE, patients underwent CTC. MR images were acquired with 1.5T MRI using the "jelly method" (ultrasonographic gel) to enable better visualisation of the dome and fornices of the vagina, rectovaginal septum, posterior compartment pelvic spaces. CTCs were performed in 3 facilities associated with the centre. Slice collimation was 3 mm with a reconstruction interval of 1.5 mm. Image analysis was performed using a dedicated workstation, allowing for the combination of 2- and 3-dimensional reviews, displayed in 4 different fly-throughs for both prone and supine scans. Patients had a laxative the day before. Colon distension was obtained after placing a rectal catheter for CO_2 insufflation using a continuous gaseous pressure. CTC and MRI reports were provided by radiologists with extensive backgrounds in the diagnosis of DIE, who were aware that colorectal endometriosis was suspected but blinded to the results of other imaging tests. All clinical and imaging information was analysed by a senior gynaecologic surgeon to decide on appropriate surgery or expectative management. Preoperative MRI, CTC, and MRI + CTC (parallel testing) reports were	****No 2x2 data**** **Diagnosis of rectal nodules** **MRI** Sensitivity: 83.6% (71.9, 91.8) Specificity: 90% (55.5, 99.7) **CTC** Sensitivity: 77.1% (64.5, 86.8) Specificity: 100% (69.2, 100) **MRI + CTC** Sensitivity: 98.4% (91.2, 99.9) Specificity: 90% (55.5, 99.7) **Diagnosis of sigmoid nodules** **MRI** Sensitivity: 54.6% (32.2, 75.6) Specificity: 93.9% (83.1, 98.7) **CTC** Sensitivity: 86.4% (65.1, 97.1) Specificity: 95.9% (86.0, 99.5) **MRI + CTC** Sensitivity: 86.4% (65.1, 97.1) Specificity: 89.8% (77.8, 96.6)	The current study suggests that combining MRI and CTC leads to greater accuracy in preoperative assessment of colorectal endometriosis. This combination provides useful information for planning surgery and for preoperative informing of patients. Our study has several limitations. First, the low number of patients included in the study may impact the statistical power of our analysis. Second, the purpose of our study was to evaluate whether combining CTC with MRI improves diagnosis and not to compare the 2 imaging techniques. MRI is indeed an excellent tool, providing a complete cartography of pelvic endometriosis implants located on various organs, not only on the digestive tract. Although our study suggests that CTC accuracy for sigmoid endometriotic nodules may surpass that of an MRI, it would be premature to conclude that a CTC could replace an MRI in preoperative assessment of patients with rectosigmoid nodules. Finally, imaging exams were preformed solely by 1 expert radiologist, preventing assessment of interobserver variability.	Patient selection: **Unclear** Index Test: **Low** Reference Standard: **High** Flow and Timing: **Unclear** Potential applicability/ directness issues: **Not all patients with DIE undergo surgery; referral centre therefore more likely to see complex/ severe cases; single centre; focus is on nodules rather than patients.** Overall risk of bias: **High and small sample size**

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 15)
			compared with intraoperative findings. Using parallel testing, MRI + CTC were considered positive if either test was positive with a consecutive increase in sensitivity and decrease in specificity.			
Full citation Ferrero et al. 2017 **Country** Italy **Study type** Prospective *See Table 8*	**Population** Patients with clinical suspicion of rectosigmoid endometriosis **Sample size** 70 included *See Table 8*	Index test 1 RWC-TVS with simple BP Index test 2 16-section CTC with air distension and no iodinated contrast Reference standard Laparoscopy with histological examination Prior tests Symptoms and clinical examination	All patients had RWC-TVS then CTC within 1–3 weeks. CTC was performed by a radiologist with more than 5 years' experience in virtual colonoscopy scans and in the diagnosis of intestinal endometriosis, using a 16-section multidetector CT scanner (LightSpeed 16; GE Medical Systems) with patients in the supine and prone positions. Efforts were made to decrease the CT radiation dose. Before CTC, patients followed a low-residue diet for 3 days. On the day before CTC, patients had a liquid diet, an intestinal preparation and fecal tagging. A standardised examination protocol was used. A 12-Fr Foley catheter was introduced by the radiologist into the distal rectum before the scan and the colon was manually dilated with room air.	****No 2x2 data**** **Rectosigmoid endometriosis (n=70) CTC** Sensitivity: 92.5% (79.6, 98.4) Specificity: 86.7% (69.3, 96.2) **Multifocal rectosigmoid endometriosis (n=70) CTC** Sensitivity: 40.0% (5.3, 85.3) Specificity: 91.4% (76.9, 98.2) *See Table 8 for other tests*	*See Table 8*	Overall risk of bias: **High and small sample size**
Full citation Zannoni et al. 2017 **Country** Italy **Study type** Prospective *See Table 8*	**Population** Patients with clinical suspicion of DIE **Sample size** 103 eligible patients, 47 who underwent both complete diagnostic examination and surgery *See Table 8*	Index test 1 TVS without BP, including transabdominal scan Index test 2 64-row CTC with air distension and iodinated contrast Reference standard Laparoscopic surgery with histological confirmation (within 1-month)	TVS and CTCU were performed independently by different experienced operators who were only aware of the suspicion of posterior compartment endometriosis. For CTCU a 64-row CT scanner (VCT Lightspeed 64, GE Healthcare) was used, following a standardised protocol. A 24 Foley rectal catheter was placed to achieve colonic distension by introducing air. Patients were scanned in the supine position through the diaphragm to the public symphysis, then in prone. Before CTCU, patients had a low fibre diet for 3 days and a laxative the day before.	****No 2x2 data**** **Presence of intestinal DIE CTCU (n=47)** Sensitivity: 78.0% Specificity: 50.0% **Presence of right ureteral DIE CTCU (n=47)** Sensitivity: 60.0% Specificity: 70.2% **Presence of left ureteral DIE CTCU (n=47)** Sensitivity: 57.1% Specificity: 76.9%	*See Table 8*	Overall risk of bias: **High and small sample size**

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 15)
		Prior tests Symptoms and gynaecological examination		*See Table 8 for other tests*		
Full citation Baggio et al. 2016. **Country** Italy **Study type** Prospective *See Table 6*	**Population** Patients suspected of deep infiltrating endometriosis enrolled to undergo surgical treatment **Sample size** 37 patients for computed tomography colonography (CTC) *See Table 6*	Index test 1 CA 125 >35 µg/mL Index test 2 TVS (without BP) Index test 3 64-rwo CTC with CO_2 distension and iodinated contrast Index test 4 Intestinal symptoms Reference standard Laparoscopic findings and subsequent pathological confirmation	CTC using a Philips Brilliance CT 64-channel scanner. After a colon preparation with diet and Movicol, oral Gastrografin was administered. Three hours later, imaging was performed after patient-controlled insufflation with CO_2 for colonic distension, with the patient in prone and supine position. 3D image reconstruction was carried out to allow visualisation of rectum and colon lumens and volumes. The CTC findings were evaluated by two senior radiologists blinded to the patients' clinical data and to the results of biologic tests and other imaging techniques. Bowel endometriosis was suspected in the presence of one or more of the following: extrinsic mass effect on the bowel wall, shortening, tethering or flattening of the bowel wall, retraction of the mucosa, or a combination of these factors.	****2x2 available**** **CTC** Sensitivity: 0.68 Specificity: 0.67 *See Table 6 for other tests*	*See Table 6*	Overall risk of bias assessment: **High and small sample size for CTC**
Full citation Biscaldi E, Ferrero S, Maggiore ULR, Remorgida V, Venturini PL, Rollandi GA. Multidetector computerized tomography enema versus magnetic resonance enema in the diagnosis of rectosigmoid endometriosis. Eur J Radiology. 2014. 83:261-267. **Country** Italy **Aim** To compare the accuracy of	**Population** Women with symptoms suggestive of rectosigmoid endometriosis **Sample size** 260 women. 67.7% had rectosigmoid endometriotic nodules. **Setting** Referral endometriosis center **Subgroup analysis** None **Inclusion criteria** Reproductive age; suspicion of deep pelvic endometriosis on the basis of gynecological	Index test 1 64-row MDCT with water distension and iodinated contrast Index test 2 1.5-T MRI with ultrasonographic gel distension Reference standard Histologically confirmed rectosigmoid endometriosis	For MDCT-3, patients had a low-residue diet for 3 days before the exam and a laxative on the day of the exam. Retrograde colonic distention was performed on the CT bed using a water enema. Patients were scanned on a 64 row MDCT scanner (LightSpeed VCT, GE Medical Systems). The scan parameters were: 64 × 0.625 mm collimation, rotation time 0.5 s, tube voltage 120 kV, effective mA 340. The injection of the contrast medium was performed accordingly to the 'double split' bolus technique. MRI-e was carried out on the following day using a 1.5-T magnet (Signa Excite HDx, GE Medical Systems) using an 8	****No 2x2 data**** **Diagnosis of rectosigmoid endometriosis (n=260)** **MDCT-e** Sensitivity: 98.3% Specificity: 98.8% **MRI-e** Sensitivity: 97.2% Specificity: 96.4%	This prospective study demonstrates that both MDCT-e and MRI-e are accurate in the diagnosis of rectosigmoid endometriosis. MDCT-e has the disadvantage of the use of ionizing radiation and iodinated contrast medium in a population of women of reproductive age. The request of the clinician to ideally evaluate the whole colon should be balanced with the fact that the incidence of intestinal endometriosis in the right, transverse and descending colon is low. MRI-e is more tolerable than MDCT-e; it is a study focused on the pelvis and on the sigmoid and	Patient selection: **Unclear** Index Test: **Low** Reference Standard: **High** Flow and Timing: **Low** Potential applicability/ directness issues: **Not all patients with rectosigmoid endometriosis undergo surgery; referral centre therefore more likely**

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 15)
multidetector computerized tomography enema (MDCT-e) and magnetic resonance enema (MRI-e) in determining the presence of sigmoid and rectal endometriotic nodules **Study type** Prospective **Study dates** Not reported **Source of funding** Not reported.	symptoms and vaginal examination; presence of GI symptoms that might be caused by rectosigmoid endometriosis. **Exclusion criteria** Previous bilateral ovariectomy; previous radiological exams of the bowel requiring contrast media; previous bowel surgery (except appendectomy); previous episodes suggestive of intolerance to iodinated contrast media; renal or hepatic failure; presence of absolute contraindications to MR examination; psychiatric disorders.	Prior tests Symptoms and clinical examination	channels phased array coil. All studies followed an established examination protocol. Ultrasonographic gel was introduced to distend the rectum and the sigmoid colon by using a syringe connected to a 20-Fr Foley catheter. The examination position of the patient was preferably prone. All patients underwent laparoscopy within one month from the radiological investigations independently from the radiological findings. The surgeon was aware of presence/absence of intestinal endometriosis in the radiological examinations. Findings of MDCT-e and MRI-e were compared with surgical and histological results.		rectum, is has satisfying sensitivity and specificity in identifying nodules in the distal colon. Future studies should aim to improve the evaluation of the patients to better understand when MDCT-e may be advisable in order to perform a whole evaluation of the colon. A potential limitation of the current study consists in the fact that a distension of the whole colon was performed during MDCT-e while only the rectosigmoid was distended during the MRI-e. Another limitation of the study is that the two techniques were not used to diagnose pelvic endometriosis but only rectal and sigmoid nodules.	**to see complex/ severe cases; single centre.** Overall risk of bias: **High**
Full citation Iosca S, Lumia D, Bracchi E, Duka E, De Bon M, Lekaj M,Uccella S, Ghezzi F, Fugazzola C. Multislice computed tomography with colon water distension (MSCT-c) in the study of intestinal and ureteral endometriosis. Clinical Imaging. 2013. 37:1061-1068. **Country** Italy **Aim** To evaluate the accuracy and reproducibility of MSCT-c in diagnosing bowel and ureteral endometriosis. **Study type** Retrospective **Study dates** Sep 2007 to Aug 2011	**Population** Women suspected of bowel endometriosis **Sample size** 94 women evaluated using MSCT-c; 64 underwent both scans and laparoscopic surgery. 85.9% had endometriotic lesions. **Setting** Not reported. Authors affiliated with a university hospital. **Subgroup analysis** Location of endometriosis **Inclusion criteria** All patients had symptoms associated with endometriosis (dysmenorrhoea, dyspareunia, CPP, and infertility) and GI symptoms suggestive of bowel endometriosis (diarrhea, rectal pain associated with	Index test 64-row MSCT with water distension and iodinated contrast Reference standard Videolaparoscopy and histological examination Prior tests Symptoms. Exam not reported.	TVS was performed in all patients before MSCT-c evaluation. Preparation for MSCT-c included a low-residue diet and administration of polyethylene glycol the day before the exam. All MSCT-c exams were performed with a 64-row scanner (Aquilon 64); the scan parameters were as follows: 64×0.5-mmcollimation, rotation time 0.5 s, tube voltage 120 kV, and automatic exposure control dose modulation system. Colonic water distension was achieved by placing a rectal Foley catheter and administering warm water. All patients received iodine contrast medium. MSCT-c images of the 64 patients that underwent both CT scan and videolaparoscopic surgery were reevaluated retrospectively by two experienced radiologists independently and in consensus. The radiologists were not aware of the surgery and histology findings.	****2x2 in text**** **Detecting bowel endometriosis** Sensitivity: 100% Specificity: 97.6% **Detecting ureteral endometriosis** Sensitivity: 72.2% Specificity: 100%	Multislice CT-c has proven to be an accurate and reproducible imaging modality, able to provide precise information regarding the location and extent of endometriotic intestinal/ureteral lesions so as to suggest the most adequate surgical treatment. The main limitation of our study consists in the radiation dose delivered to each patient, although our results show a significant dose reduction when exams were carried out with split-bolus technique compared to those performed with two postcontrast scans…; this limit is not negligible, considering the young age of the patients and their desire for future pregnancies. …Finally, the low intrinsic contrast resolution of MSCT-c exams creates difficulties in the detection of other endometriotic lesions that are often associated, in particular those of the	Patient selection: **Unclear** Index Test: **Low** Reference Standard: **Unclear** Flow and Timing: **Unclear** Potential applicability/ directness issues: **Not all patients with endometriosis undergo surgery.** Overall risk of bias: **High and small sample size**

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 15)
Source of funding The authors have disclosed that they have no financial relationships with or interests in any of the following organizations: National Institutes of Health, Wellcome Trust, and Howard Hughes Medical Institute.	menses, constipation, and dyschezia). **Exclusion criteria** Not reported.		Histological examination was considered to be the standard of reference for both intestinal and ureteral locations.		rectovaginal septum and the uterosacral ligaments. It is therefore currently considered preferable, in view of the type of patients (women in their reproductive age), the use of MRI-c; MSCT-c, carried out with split bolus technique, should be reserved to those patients who are unable to accept the higher discomfort of MRI-c examination.	
Full citation Stabile Ianora AA, Moschetta M, Lorusso F, Lattarulo S, Telegrafo M, Rella L, Scardapane A. Rectosigmoid endometriosis: Comparison between CT water enema and video laparoscopy. Clinical Radiology. 2013. 68:895-901. **Country** Italy **Aim** To evaluate the accuracy of water enema CT for predicting the location of endometriosis in patients with contraindications to MRI, focusing on rectosigmoid lesions. **Study type** Prospective **Study dates** May 2009 to Dec 2010 **Source of funding** Not reported	**Population** Consecutive women with clinical suspicion of deep pelvic and bowel endometriosis and contraindication to MRI **Sample size** 33 women. 69% intestinal endometriotic implants; 31% endometriosis without bowel involvement. **Setting** Not reported. Authors affiliated with a university medical school. **Subgroup analysis** None **Inclusion criteria** Clinical symptoms (e.g. CPP, dysmenorrhoea, dyspareunia, and infertility); GI disorders suggestive of bowel involvement; defecation disorders without signs of bowel obstructions; difficult and painful rectosigmoid endoscopy because of anomalous narrowing of bowel lumen due to extrinsic compression; video laparoscopy within 4 weeks of CT exam; contraindications to MRI.	Index test 64-row CT with water distension and water contrast Reference standard Laparoscopic and histological findings Prior tests History and physical exam	Two radiologists with 15 and 5 years of experience in abdominal imaging, who were blinded to the clinical data and to the results of the other, evaluated the CT images. A low residue diet was observed for 3 days before CT. The day before, intestinal preparation involved ingestion of polyethylene glycol and a liquid diet. A 24 Foley rectal catheter was placed and colonic distension was achieved by introducing water; patients were scanned in the supine position from the dome of the diaphragm to the pubic symphysis. A 64-row CT machine (Aquilion One, Toshiba) was used with the following protocol: detector collimation 64 x 0.5 mm, rotation time 0.5 s, 120 kV, and 200mAs. CT findings were compared with laparoscopic and histological findings. Laparoscopic surgery was performed by a surgeon with 15 years of experience in abdominal video laparoscopy. All specimens obtained were evaluated histologically for the presence of endometriotic tissue, particularly focusing on intestinal wall involvement.	****2x2 in text**** **Diagnosis of bowel endometriosis** Sensitivity: 87% Specificity: 100%	Diagnosis of rectosigmoid endometriosis should always be considered in cases of young women affected by recurrent abdominal pain and gastrointestinal symptoms, particularly at the end of the ovarian cycle. Therefore, diagnostic, non-invasive imaging is justified in order to detect the real incidence of bowel endometriotic implants. Based on the results obtained, CT examination can play a role in the diagnosis of bowel endometriosis when retrograde colonic water distension is used; CT represents another potential method for the evaluation of this condition, especially in patients for whom MRI is contraindicated.	Patient selection: **Low** Index Test: **Low** Reference Standard: **Unclear** Flow and Timing: **Low** Potential applicability/ directness issues: **Not all patients with bowel endometriosis undergo surgery.** Overall risk of bias: **High and very small sample size**

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 15)
	Exclusion criteria Did not undergo video laparoscopy within 4 weeks of the imaging.					
Full citation Biscaldi E, Ferrero S, Remorgida V, Rollandi GA. MDCT enteroclysis urography with split-bolus technique provides information on ureteral involvement in patients with suspected bowel endometriosis. AJR. 2011. 196:W635-W640. **Country** Italy **Aim** To evaluate the accuracy of MDCT enteroclysis with a split-bolus technique in detecting ureteral compression caused by endometriosis in women with suspected bowel endometriosis. **Study type** Prospective **Study dates** Not reported **Source of funding** Not reported	**Population** Women with suspected bowel endometriosis **Sample size** 106 were considered, **103** included. 65.0% had bowel endometriotic nodules, 30.1% had only pelvic endometriosis. **Setting** Not reported. Authors affiliated with hospitals and a university. **Subgroup analysis** Ureteral compression **Inclusion criteria** Pain symptoms caused by pelvic endometriosis (i.e. dyspareunia, dysmenorrhoea, CPP) and gastrointestinal complaints suggestive of colorectal endometriosis. **Exclusion criteria** Previous diagnosis of urolithiasis; diminished renal function; pregnancy; contraindication to CT (including allergies to contrast medium).	Index test 16-MDCT enteroclysis urography with iodinated contrast Reference standard Laparoscopy and histological confirmation Prior tests Clinical findings	Before MDCT, patients had low-residue diet for 3 days. The day before, administered polyethylene glycol. Colonic distension achieved by introducing warm water. Iodinated contrast received using split-bolus technique. Scanning performed in the supine position from the dome of the diaphragm to pubic symphysis using a 16-MDCT scanner (LightSpeed, GE Healthcare). Tube voltage was 120 kVp, rotation time 0.7 sec, collimation 16 × 0.625 mm, effective slice thickness 5 mm. All images were independently evaluated by two radiologists with ≥10 years experience in interpreting abdominal CT. In cases of disagreement between the two radiologists, images were evaluated in consensus. Radiologists were not aware of clinical findings and findings from previous radiologic examinations and knew only that bowel endometriosis with potential ureteral involvement was suspected. All subjects underwent laparoscopy within 1 month after MDCT enteroclysis. Surgery was performed by a team of gynecologic and colorectal surgeons with extensive experience in treatment of pelvic and bowel endometriosis, who were informed about the presence and characteristics of bowel endometriotic lesions, but not the urologic findings of MDCT enteroclysis urography. All specimens excised at surgery were histopathologically evaluated.	****2x2 in text**** **Identifying bowel nodules** Sensitivity: 95.5% Specificity: 97.2% **Diagnosing bowel nodules infiltrating at least the muscular layer** Sensitivity: 93.3% Specificity: 96.6% **Identifying ureteral compression** Sensitivity: 97.1% Specificity: 98.8%	MDCT enteroclysis urography has an elective application in women with suspected bowel endometriosis not only because it allows diagnosis of ureteral compression caused by endometriosis but also because it does not compromise the accuracy of MDCT enteroclysis in the detection of bowel endometriotic nodules. Although we did not compare MDCT enteroclysis urography with other techniques, our data show that sensitivities and specificities in detecting bowel and ureteral endometriosis are comparable to those of other protocols. The strong NPVs provided by MDCT enteroclysis urography suggest that ureteral compression caused by endometriosis and bowel nodules infiltrating the muscularis propria are extremely unlikely in the setting of a negative examination. This finding is particularly relevant because these two variables affect the technical complexity of surgery and the risk of postoperative complications. Of importance is that investigating the urinary tract using MDCT enteroclysis urography does not increase the radiation dose imparted to the patient when compared with MDCT enteroclysis. Given the significant advantages of MDCT enteroclysis urography in the preoperative evaluation of women with suspected bowel endometriosis, we believe that other authors should evaluate its effectiveness.	Patient selection: **Unclear** Index Test: **Low** Reference Standard: **High** Flow and Timing: **Low** Potential applicability/ directness issues: **Not all patients with bowel endometriosis undergo surgery.** Overall risk of bias: **High**

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 15)
Full citation Ferrero S, Biscaldi E, Morotti M, Venturini PL, Remorgida V, Rollandi GA, Valenzano Menada M. Multidetector computerized tomography enteroclysis vs. rectal water contrast transvaginal ultrasonography in determining the presence and extent of bowel endometriosis. Ultrasound Obstet Gynecol. 2011. 37:603-613. **Country** Italy **Aim** To compare the accuracy of MDCT-e and RWC-TVS in determining the presence and extent of bowel endometriosis. **Study type** Prospective **Study dates** Jan 2008 to Nov 2009 **Source of funding** Not reported	**Population** Women with suspected bowel endometriosis **Sample size** 96 included. 53.1% had bowel endometriotic nodules, 37.5% had only pelvic endometriosis. **Setting** Endometriosis referral centre **Subgroup analysis** Bowel Rectosigmoid **Inclusion criteria** Referred for suspicion of deep pelvic endometriosis (on basis of gynecological symptoms and vaginal examination); presence of GI symptoms that might be caused by bowel endometriosis; reproductive age; desire to undergo complete surgical excision of endometriosis. **Exclusion criteria** Previous bilateral ovariectomy; previous barium radiological examination or other examination for the diagnosis of bowel endometriosis; previous bowel surgery; previous episodes suggestive of intolerance to iodinated contrast medium; renal or hepatic failure; and psychiatric disorders.	Index test 1 16-row MDCT-e with iodinated contrast Index test 2 RWC-TVS with BP[23] Reference standard Laparoscopic surgery with histological confirmation Prior tests Symptoms and vaginal examination	MDCT-e and RWC-TVS were independently and blindly performed by different investigators. The two radiologists and the two ultrasonographers were blinded to the clinical data and knew only that the presence of intestinal endometriosis was suspected. Before MDCT-e, patients had a low-residue diet for 3 days, and a laxative the day before. Patients were examined with a 16-row MDCT scanner (LightSpeed, GE Medical Systems). The scan parameters were: 16 × 0.625 mm collimation, rotation time 0.6 s, tube voltage 120 kV; maximum mA peak was 370 mA. Patients were scanned in the supine position; after the injection of the intravenous iodinated contrast medium. Before RWC-TVS, patients had a low-fibre diet for 3 days and a rectal enema within a few hours before the procedure. RWC-TVS was performed using a Siemens Sonoline Antares ultrasound machine (Siemens Medical) and a Voluson i ultrasound machine (GE Healthcare Ultrasound) connected to transvaginal transducers. A 18Ch flexible catheter was used to introduce warm saline into the rectum and sigmoid. All patients underwent laparoscopy within 1 month from the completion of the diagnostic investigations. The findings of MDCT-e and RWC-TVS were compared with histological results.	****2x2 in text**** **Diagnosis of bowel endometriosis** **MDCT-e (n=96)** Sensitivity: 96.1% Specificity: 100% **RWC-TVS (n=96)** Sensitivity: 88.2% Specificity: 97.8% **Diagnosis of rectosigmoid endometriosis** **MDCT-e (n=96)** Sensitivity: 95.8% Specificity: 100% **RWC-TVS (n=96)** Sensitivity: 93.8% Specificity: 97.9%	This study has shown that RWC-TVS is a reliable technique for determining the presence and extent of rectosigmoid endometriosis and that it has an accuracy similar to that of MDCT-e. However, RWC-TVS may sometimes underestimate the presence of multiple bowel nodules. RWC-TVS can be performed easily in an ambulatory setting and it is well tolerated by patients. MDCT-e may still have a role in the diagnostic workup of patients with suspected bowel endometriosis. When TVS or RWC-TVS demonstrates large intestinal nodules infiltrating the bowel muscularis, bowel resection can probably be performed without further investigation unless the surgeon wants to exclude intestinal lesions located proximally to the sigmoid. In contrast, when ultrasonography demonstrates a single bowel nodule that may be excised by nodulectomy, MDCT-e should be used to exclude the presence of other intestinal nodules and, thus, to adequately plan the surgical procedure with the colorectal surgeon and the patient.	Patient selection: **Unclear** Index Test: **Low** Reference Standard: **Unclear** Flow and Timing: **Low** Potential applicability/ directness issues: **Not all patients with bowel endometriosis undergo surgery.** Overall risk of bias: **High and small sample size**

[23] The results from RWC-TVS are not shown with other TVS results because ths study was included in the NICE 2017 Guideline for TVS (but not CT).

Abbreviations: BP, bowel preparation; CO_2, carbon dioxide; COI, conflict of interest; CT, computed tomography; CTC, computed tomography colonoscopy; CTCU, computed tomography colonography with contrast media and urographic phase; DIE, deep infiltrating endometriosis; GI, gastrointestinal; MDCT, multidetector computerised tomography; MDCT-e, multidetector computerised tomography enema; MRI, magnetic resonance imaging; MRI-c , MRI with water distension of the colon; MRI-e, magnetic resonance enema; MSCT-c, multislice computed tomography with colon water distension; RWC-TVS, rectal water contrast transvaginal ultrasonography.

Table 15 QUADAS-2 Diagnostic accuracy checklist: Diagnosis of endometriosis – computed tomography

Domain	Question	Mehedintu 2018	Biscaldi 2014	Iosca 2013	Stabile Ianora 2013	Biscaldi 2011	Ferrero 2011
Patient selection							
Signalling questions	Was a consecutive or random sample of patients enrolled?	Unclear (not reported)	Unclear (not reported)	Unclear (not reported)	Yes	Unclear (not reported)	Unclear (not reported)
	Was a case-control design avoided?	Yes	Yes	Yes	Yes	Yes	Yes
	Did the study avoid inappropriate exclusions?	Unclear (not reported)	Yes	Unclear (not reported)	Yes	Yes	Yes
Risk of Bias	**Could the selection of patients have introduced bias?**	**Unclear**	**Unclear**	**Unclear**	**Low**	**Unclear**	**Unclear**
Concerns regarding applicability	Are there concerns that the included patients and setting do not match the review question?	High (referral centre more likely to see complex/ severe cases; single centre)	High (referral centre more likely to see complex/ severe cases; single centre)	Unclear	Unclear	Unclear	High (referral centre more likely to see complex/ severe cases; single centre)
Index Test							
Signalling questions	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	Yes	Yes	Yes	Yes	Yes
	If a threshold was used, was it pre-specified?	N/A	N/A	N/A	N/A	N/A	N/A
Risk of bias	**Could the conduct or interpretation of the index test have introduced bias?**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
Concerns regarding applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear (very experienced technicians/clinicians performing the tests)	Unclear (very experienced technicians/clinicians performing the tests)	Unclear (very experienced technicians/clinicians performing the tests)	Unclear (very experienced technicians/clinicians performing the tests)	Unclear (very experienced technicians/clinicians performing the tests)	Unclear (very experienced technicians/clinicians performing the tests)
Reference Standard							
Signalling questions	Is the reference standard likely to correctly classify the target condition?	Unclear (intraoperative findings of nodule characteristics)	Yes	Unclear (criteria for diagnosis not reported)	Yes	Yes	Yes

Domain	Question	Mehedintu 2018	Biscaldi 2014	Iosca 2013	Stabile Ianora 2013	Biscaldi 2011	Ferrero 2011
	Were the reference standard results interpreted without knowledge of the results of the index tests?	No	No	Unclear (information not reported)	Unclear (information not reported)	No[24]	Unclear (information not reported)
Risk of Bias	**Could the reference standard, its conduct, or its interpretation have introduced bias?**	**High**	**High**	**Unclear**	**Unclear**	**High**	**Unclear**
Concerns regarding applicability	Are there concerns that the target condition as defined by the reference standard does not match the question?	High (not all patients will undergo surgery; detection of nodules rather than patients)	High (not all patients will undergo surgery)	High (not all patients will undergo surgery)	High (not all patients will undergo surgery)	High (not all patients will undergo surgery)	High (not all patients will undergo surgery)
Flow and Timing							
Signalling questions	Was there an appropriate interval between index test and reference standard?	Unclear (specific timeframe not mentioned)	Yes (MDCT-e and MRI-e performed within 2 days; laparoscopy within 1 month from radiological investigations)	Unclear (specific timeframe not mentioned)	Yes (laparoscopy within 4 weeks of CT exam)	Yes (laparoscopy within 1 month after MDCT enteroclysis urography)	Yes (videolaparoscopy within 4 weeks of CT)
	Did all patients receive a reference standard?	Yes	Yes	Yes	Yes	Yes	Yes
	Did all patients receive the same reference standard?	Unclear (different surgical procedures[25])	Yes	Yes	Yes	Yes	Yes
	Were all patients included in the analysis?	Yes	Yes	Yes	Yes	Yes	Yes
Risk of Bias	**Could the patient flow have introduced bias?**	**Unclear**	**Low**	**Unclear**	**Low**	**Low**	**Low**

Abbreviations: CT, computed tomography; MDCT, multidetector computerised tomography; MDCT-e, multidetector computerised tomography enema; MRI, magnetic resonance imaging; MRI-e, magnetic resonance enema; N/A, not applicable.

Note: Risk of Bias assessment for Ferrero et al. 2017 is located in Table 9. Risk of Bias assessment for Zannoni 2017 is located in Table 11. Risk of Bias assessment for Baggio et al 2016 is located in Table 7.

[24]Surgeons were informed about the presence and characteristics of bowel endometriotic lesions; however, they were not informed about the urologic findings of MDCT enteroclysis urography.

[25] All information provided by clinical and imaging techniques was subsequently analysed by a senior gynaecologic surgeon to decide on the appropriate surgical technique (shaving, disc excision, colorectal resection, or expectative management)

Magnetic resonance imaging

Table 16 Evidence Summary: Diagnosis of endometriosis – magnetic resonance imaging

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 15)
Full citation Berger et al. 2019. **Country** The Netherlands **Study type** Prospective *See Table 6*	**Population** Patients with a clinical suspicion of endometriosis **Sample size** 72 underwent the full diagnostic pathway: i.e. history, clinical examination, dynamic TVUS, and MRI. *See Table 6*	Index test 1 History Index test 2 History + clinical exam Index test 3 History + clinical exam + dynamic TVUS (without BP) Index test 4 History + clinical exam + dynamic TVUS (without BP) + 1.5T-MRI (no BP, no contrast) Reference standard Visual diagnosis at laparoscopy with histological confirmation	MRI was performed within 6 weeks after dynamic TVUS. MRI was performed using a 1.5-T superconducting magnet (Magnetom Avantofit; Siemens AG) using an 18-channel radiofrequency body coil. The MRI protocol consisted of multiplanar turbo spin echo T2-weighted images (512 matrix; axial, sagittal, and coronal with a voxel size of 0.8 × 0.8 × 4.0 mm) and axial and sagittal T1-weighted fat-saturated breath hold sequences (320 matrix; voxel size of 1.3 × 1.3 × 6.0 mm. No enema was administered; no vaginal distention was applied; and patients did not fast. No contrast agent was used. All MRI examinations were evaluated by a single radiologist with 10 years of experience in endometriosis, blinded to the results of the history, clinical examination, and dynamic TVUS.	****No 2x2 data**** **Endometriosis** **History + clinical exam + TVUS + MRI (n=72)** Sensitivity: 85.9% Specificity: 62.5% p-value NS compared to previous step [26] **DIE** **History + clinical exam + TVUS + MRI (n=72)** Sensitivity: 88.1% Specificity: NN p-value NS compared to previous step [27]	*See Table 6*	Overall risk of bias assessment: **High and small sample size**
Full citation Chen et al. 2019 **Country** China **Study type** Retrospective *See Table 6*	**Population** Patients with suspected RVE **Sample size** 29 consecutive patients *See Table 6*	Index test 1 Physical examination (bimanual and trimanual) Index test 2 TVS (without BP) Index test 3 Pelvic 3.0T-MRI with gadolinium-based contrast Index test 4 RES (with rectal lavage)	All patients underwent MRI using a 3.0-T whole-body MRI device (GE Signa) with a multichannel phase array coil. The women were requested to fast for at least 4 hours before the examination was started, and a gadolinium-based contrast agent was administered intravenously. The following sequences were used: T1- and T2-weighted turbo spin-echo images in axial, sagittal, and coronal planes; matrix, 128 x 128; slice number, 20; and slice thickness, 5 mm.	****No 2x2 data**** **Diagnosis of RVE MRI** Sensitivity: 90.5% (68.2, 98.3) Specificity: 87.5% (46.7, 99.3) **Identification of rectal infiltration MRI** Sensitivity: 73.3% (44.8, 91.1) Specificity: 92.9% (64.2, 99.6)	*See Table 6*	Overall risk of bias assessment: **High and very small sample size**

[26] The added value of MRI compared to history + clinical exam was significant (p<0.001)
[27] The added value to MRI compared to history + clinical exam was significant (p<0.001)

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 15)
		Reference standard Surgical and histologic findings Prior tests Clinical history and physician's clinical findings				
Full citation Hernandez Gutierrez et al. 2019 **Country** Spain **Study type** Retrospective *See Table 10*	**Population** Patients who presented with clinical suspicion of DIE **Sample size** 69 eligible presented, **48** fulfilled inclusion criteria. 100% had DIE *See Table 10*	Index test 1 2D-TVUS plus transabdominal ultrasound with BP Index test 2 MRI with BP Reference standard Laparoscopic surgery with histological confirmation Prior tests Gynaecologic examination	MRI was performed by a radiologist skilled in abdominal and pelvic radiology for endometriosis, who was blinded to the ultrasound results, using a 1.5T MRI device (GE Signa Explorer; GE Healthcare). Bowel preparation before MRI involved one dose of Puntualex with abundant hydration every 8 hours, 3 days prior to the procedure. Sonographic gel was introduced into the vagina and to distend the rectum and sigmoid colon.	****No 2x2 data**** **Rectovaginal space (n=48)** **MRI** Sensitivity: 74% Specificity: 64% **Vagina (n=48)** **MRI** Sensitivity: 33% Specificity: 93% **Utero-sacral ligaments (n=48)** **MRI** Sensitivity: 67% Specificity: 43% **Rectosigmoid (n=48)** **MRI** Sensitivity: 69% Specificity: 87% **Bladder (n=48)** **MRI** Sensitivity: 67% Specificity: 100% **Ureter (n=48)** **MRI** Sensitivity: 33% Specificity: 98% *See Table 10 for other tests*	*See Table 10*	Overall risk of bias: **High and small sample size**
Full citation Alborzi et al. 2018 **Country** Iran **Study type** Prospective	**Population** Consecutive patients with signs and symptoms of endometriosis **Sample size** 317 enrolled	Index test 1 2D-TVUS with BP Index test 2 TRS with BP Index test 3 1.5-T MRI with lubricant gel and	All MRI evaluations were reported by a certified radiologist with MRI fellowship, blinded to history and physical examination. MRI was performed before and after injection of gadolinium contrast medium using 1.5 Tesla (Avento Seimens Machine) through the body pelvic but not	****2x2 available**** **All DIE lesions (n=317)** **MRI** Sensitivity: 90.4% Specificity: 66.1%	*See Table 8*	Overall risk of bias: **High**

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 15)
See Table 8	79.5% had DIE, 20.5% had no lesion. *See Table 8*	gadolinium contrast Reference standard Laparoscopy with histological examination Prior tests Clinical symptoms and physical examination	endovaginal coil, with lubricant gel inserted into the vaginal cuff and hyoscine intramuscular injection for better delineation.	**Uterosacral ligaments (n=317)** **MRI** Sensitivity: 63.58% Specificity: 93.98% **Rectal wall (n=317)** **MRI** Sensitivity: 76.92% Specificity: 96.6% **Ovarian fossa (n=317)** **MRI** Sensitivity: 66.1% Specificity: 98.06% **Retrocervical (n=317)** **MRI** Sensitivity: 65.79% Specificity: 96.42% **Rectovaginal septum (n=317)** **MRI** Sensitivity: 72.73% Specificity: 95.24% **Bladder (n=317)** **MRI** Sensitivity: 100% Specificity: 99.68% **Ureter (n=317)** **MRI** Sensitivity: 100% Specificity: 100% *See Table 8 for other tests*		
Full citation Mehedintu et al. 2018 **Country** France **Study type** Retrospective *See Table 14*	**Population** Women with planned surgery for deep endometriosis infiltrating the rectum or sigmoid colon **Sample size** 71 patients underwent MRI followed by CTC for preoperative assessment *See Table 14*	Index test 1 1.5T MRI with ultrasonographic gel Index test 2 CTC with CO_2 insufflation Index test 3 MRI + CTC Reference standard Intraoperative	MR images were acquired with 1.5T MRI using the "jelly method" (ultrasonographic gel) to enable better visualisation of the dome and fornices of the vagina, rectovaginal septum, posterior compartment pelvic spaces. CTC and MRI reports were provided by radiologists with extensive backgrounds in the diagnosis of DIE, who were aware that colorectal endometriosis was suspected but	****No 2x2 data**** **Diagnosis of rectal nodules** **MRI** Sensitivity: 83.6% (71.9, 91.8) Specificity: 90% (55.5, 99.7) **Diagnosis of sigmoid nodules** **MRI**	*See Table 14*	Overall risk of bias: **High and small sample size**

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 15)
		findings (surgical and histological records)	blinded to the results of other imaging tests.	Sensitivity: 54.6% (32.2, 75.6) Specificity: 93.9% (83.1, 98.7) *See Table 14 for other tests*		
Full citation Yap SZL, Leathersich S, Lu J, Fender L, Lo G . Pelvic MRI staging of endometriosis at 3 T without patient preparation or anti-peristaltic: Diagnostic performance outcomes. Eur J Radiology. 2018. 105:72-80. **Country** Australia **Aim** To assess whether a departmental protocol using a 3 T MRI system with fast imaging acquisition, without the use of any patient preparation, contrast distension or anti-spasmodic agent achieves clinically acceptable diagnostic performance outcomes that are comparable to known international standards, and whether it adequately detects endometriotic bowel lesions to guide surgical preoperative planning. **Study type** Retrospective **Study dates** Jan 2015 to Apr 2017 **Source of funding** The authors declared no COIs.	**Population** Women with clinically suspected endometriosis **Sample size** 98 MRI studies, 61 had no surgical or pathology record, 37 underwent laparoscopy and were included **Setting** Tertiary women's hospital **Subgroup analysis** None **Inclusion criteria** Women aged 18-50 years who had a pelvic MRI using the 3-T MRI system for the indication of clinically suspected endometriosis, and who subsequently had surgery; pelvic MRI was performed to diagnose or to stage endometriosis to assist the surgical decision-making. **Exclusion criteria** Not reported	Index test 3-T MRI without contrast Reference standard Laparoscopy and histological confirmation Prior tests "clinically suspected"	MRI examinations were performed using a 3 T Siemens Skyra MRI (Siemens Medical Solutions) with an 18 channel body coil anteriorly combined with a 32 channel spine coil posteriorly. Study duration was approximately 30 min, with no patient preparation. Women were not fasted, their bladders were not emptied, and no abdominal strapping was used during the study. MRI data were then compared to each corresponding surgical report and/or pathology report as a reference standard. Average time interval from MRI report to surgical operation was 195 days.	****2x2 available**** **Any endometriosis** Sensitivity: 76.9% (69.7, 84.0) Specificity: 98.5% (97.3, 99.6) **Anterior compartment** Sensitivity: 33% (0, 86.7) Specificity: 100% (100, 100) **Posterior compartment** Sensitivity: 76.5% (66.4, 86.6) Specificity: 99.4% (98.1, 100) **Middle compartment** Sensitivity: 79.4% (69.4, 89.4) Specificity: 95.1% (91.2, 98.9) **Rectosigmoid** Sensitivity: 94.4% (83.9, 100) Specificity: 94.7% (84.7, 100) **Right ovary** Sensitivity: 100% (100, 100) Specificity: 85.0% (69.4, 100) **Left ovary** Sensitivity: 93.8% (81.9, 100) Specificity: 95.2% (86.1, 100)	Overall, the value of MRI for characterising endometriosis in our patients lies in its ability to accurately describe surgically significant bowel involvement. The majority of cases can be managed independently by gynaecological surgeons including those cases with significant adhesions and widespread superficial disease. Those cases that require further surgical expertise from colorectal specialists are those with DIE involving the bowel. Our study has confirmed the utility of 3 T MRI using rapid imaging sequences without bowel preparation in diagnosing and characterising such lesions and allowing for safe and appropriate surgical planning. One of the main limitations of this study was the long interval from MRI assessment to surgical operation (range of 5–563 days). During that period, women may have developed new lesions, resulting in a false negative MRI categorisation. Alternatively, they may have had medical management optimised (e.g. with hormonal therapy), so that lesions were reduced, and true positive MRI findings were categorised as false positive as no involvement was seen at surgery. In either case, it would have suppressed the accuracy of our analysis and resulted in underestimation of both sensitivity and specificity that we obtained	Patient selection: **Unclear** Index Test: **Low** Reference Standard: **High** Flow and Timing: **Unclear** Potential applicability/ directness issues: **Not all patients with bowel endometriosis undergo surgery; referral centre therefore more likely to see complex/ severe cases; single centre.** Overall risk of bias: **High and very small sample size**

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 15)
				Uterus Sensitivity: 86.7% (69.5, 100) Specificity: 100% (100, 100) *Also bladder, VUP, VVS, right ureter, left ureter, RFT, LFT, PoD, Torus, right USL, left USL, RVS*	from the current dataset, due to the increased number of false negatives and false positives, respectively. Due to the retrospective design, it was not possible to obtain correlation with laparoscopy or histopathology results of women who had MRI studies negative for endometriosis as most did not undergo surgery, …. This may have resulted in an overestimate in our sensitivity, due to the possibility of false negatives arising that were not detected, as well as an underestimate in specificity, due to the likelihood that surgery would have otherwise confirmed additional true negative results.	
Full citation Leone Roberti Maggiore et al. 2017 **Country** Italy **Study type** Prospective *See Table 8*	**Population** Consecutive patients referred for clinical suspicion of rectosigmoid endometriosis **Sample size** 286 who underwent both diagnostic examination and surgery. 52.8% had rectosigmoid endometriosis; 8.6% had infiltration of the mucosa *See Table 8*	Index test 1 RWC-TVS with simple BP Index test 2 Magnetic resonance enema (MR-e) Reference standard Laparoscopic surgery with histological confirmation Prior tests Symptoms with or without vaginal examination	MR-e was performed on a 1.5-T magnet (Signa Excite HDx, GE Medical Systems) using an 8-channel phased-array coil, following a standardised protocol. Retrograde distension was performed initially in the left lateral decubitus, then in the horizontal position to reduce abdominal wall movements and respiratory artifacts. Sonographic gel was introduced using a syringe connected to a 20-Fr Foley catheter to distend the rectum and the sigmoid colon. Intestinal hypotonisation was not used. The findings of MR-e and RWC-TVS were compared with surgical and histological results.	****No 2x2 data**** **Presence of rectosigmoid endometriosis MR-e (n=286)** Sensitivity: 95.4% (90.7, 99.1) Specificity: 97.8% (93.6, 99.5) **Infiltration of mucosal layer of bowel wall MR-e (n=286)** Sensitivity: 66.7% (34.9, 90.1) Specificity: 85.0% (80.3, 89.0) *See Table 8 for other tests*	*See Table 8*	Overall risk of bias: **High**
Full citation Biscaldi et al. 2014 **Country** Italy **Study type** Prospective	**Population** Women with symptoms suggestive of rectosigmoid endometriosis **Sample size** 260 women.	Index test 1 64-row MDCT with water distension and iodinated contrast Index test 2 1.5-T MRI with	MRI-e was carried out on the following day using a 1.5-T magnet (Signa Excite HDx, GE Medical Systems) using an 8 channels phased array coil. All studies followed an established examination protocol.	****No 2x2 data**** **Diagnosis of rectosigmoid endometriosis (n=176)** **MRI-e**	*See Table 14*	Overall risk of bias: **High**

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 15)
See Table 14	67.7% had rectosigmoid endometriotic nodules. *See Table 14*	ultrasonographic gel distension Reference standard Histologically confirmed rectosigmoid endometriosis Prior tests Symptoms and clinical examination	Ultrasonographic gel was introduced to distend the rectum and the sigmoid colon by using a syringe connected to a 20-Fr Foley catheter. The examination position of the patient was preferably prone.	Sensitivity: 97.2% Specificity: 96.4% *See Table 14 for other tests*		

Abbreviations: BP, bowel preparation; CO_2, carbon dioxide; COI, conflict of interest; CTC, computed tomography colonoscopy; DIE, deep infiltrating endometriosis; MDCT, multidetector computerised tomography; MRI, magnetic resonance imaging; MR-e, magnetic resonance enema; RVE, rectovaginal endometriosis; RWC-TVS, rectal water contrast transvaginal ultrasonography; TRUS, transrectal ultrasonography; TVUS, transvaginal ultrasonography.

Table 17 QUADAS-2 Diagnostic accuracy checklist: Diagnosis of endometriosis – computed tomography

Domain	Question	Yap 2018
Patient selection		
Signalling questions	Was a consecutive or random sample of patients enrolled?	Unclear
	Was a case-control design avoided?	Yes
	Did the study avoid inappropriate exclusions?	Unclear (not reported)
Risk of Bias	**Could the selection of patients have introduced bias?**	**Unclear**
Concerns regarding applicability	Are there concerns that the included patients and setting do not match the review question?	High (tertiary referral centre more likely to see complex/ severe cases; single centre)
Index Test		
Signalling questions	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
	If a threshold was used, was it pre-specified?	N/A
Risk of bias	**Could the conduct or interpretation of the index test have introduced bias?**	**Low**
Concerns regarding applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference Standard		
Signalling questions	Is the reference standard likely to correctly classify the target condition?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index tests?	No
Risk of Bias	**Could the reference standard, its conduct, or its interpretation have introduced bias?**	**High**

Domain	Question	Yap 2018
Concerns regarding applicability	Are there concerns that the target condition as defined by the reference standard does not match the question?	High (not all patients will undergo surgery)
Flow and Timing		
Signalling questions	Was there an appropriate interval between index test and reference standard?	Unclear (median 153 days; range 5-563 days)
	Did all patients receive a reference standard?	Yes
	Did all patients receive the same reference standard?	Yes
	Were all patients included in the analysis?	Yes
Risk of Bias	**Could the patient flow have introduced bias?**	**Unclear**

Abbreviations: N/A, not applicable.

Note: Risk of Bias assessments for Berger et al. 2019 and Chen et al. 2019 are located in Table 7. Risk of Bias assessments for Alborzi et al. 2018 and Leone Roberti Maggiore et al. 2017 are located in Table 9. Risk of Bias assessment for Hernandez Gutierrez et al. 2019 is located in Table 11. Risk of Bias assessments for Mehedintu et al. 2018 and Biscaldi et al. 2014 are located in Table 14.

Biomarkers

Table 18 Evidence Summary: Diagnosis of endometriosis – peripheral biomarkers

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 19)
Full citation Hirsch M, Duffy JMN, Deguara CS, Davis CJ, Khan KS. Diagnostic accuracy of Cancer Antigen 125 (CA125) for endometriosis in symptomatic women: A multi-center study. Eur J Obstet Gynecol Reprod Biol. 2017. 210:102-107. **Country** United Kingdom **Aim** To assess the diagnostic accuracy of serum Cancer Antigen 125 >30 u/ml for diagnosing endometriosis in symptomatic women **Study type** Prospective **Study dates** Oct 2013 to Mar 2015 **Source of funding** Malta Government Scholarship Grant.	**Population** Women suspected of endometriosis undergoing surgery **Sample size** 67 prospectively recruited**;** 58 in primary analysis. 51.7% had confirmed endometriosis. **Setting** 2 tertiary referral hospitals **Subgroup analysis** None **Inclusion criteria** Women referred for investigation of gynaecological pain symptoms and/or subfertility. **Exclusion criteria** Have/had a condition other than endometriosis that can raise CA 125;[28] no histological confirmation of disease *a priori*; biopsy of suspected lesions not possible; failed laparoscopic entry.	Index test CA 125 >30 µ/mL Reference standard Visualisation at laproscopy and histological confirmation Prior tests Symptoms and history	Serum samples were collected preoperatively for CA 125 immunoassay measurement. Participants underwent routine operative surgical management of endometriosis from a consultant gynecologist on the same day. Surgeons performing the procedures were blinded to the result of the CA 125 test that was processed in a certified laboratory within 4 h of sampling with an automated immunoassay. Laparoscopy was performed and all recognisable endometriosis lesions were biopsied and then treated by either coagulation, excision, or ovarian cystectomy. In accordance with ESHRE guidance[29], histological confirmation of disease was attempted but not possible in all cases of suspected endometriosis. As the diagnosis of endometriosis has poor accuracy based on visual diagnosis alone, the authors decided to exclude those participants without histological confirmation of disease a priori.	****No 2x2 data**** **CA 125** Sensitivity: 57% (95% CI 37.4, 74.5) Specificity: 96% (81.7, 99.9) Area under the curve: 0.85 (0.74, 0.96)	CA 125 >30 u/ml is highly predictive of endometriosis in women with symptoms of pain and/or subfertility. CA 125 should be considered as a rule-in test for expediting the diagnosis and management of endometriosis, CA 125 <30 u/ml is, however, unable to rule out endometriosis. The sensitivity of this test remains poor, limiting its use to cohorts of symptomatic women with a high pre-test prevalence. The high specificity minimises false positive results and unnecessary treatment exposure from hormonal therapies or surgical procedures Further research is required among a population of women with pelvic pain or subfertility and a negative pelvic ultrasound scan to assess its role in triaging treatment, access to specialist services, and reducing time to diagnosis or symptom control.	Patient selection: **Low** Index Test: **Low** Reference Standard: **Low** Flow and Timing: **Low** Potential applicability/ directness issues: **Endometriosis patients who undergo surgery may have a different profile to those who do not; level of experience of person interpreting tests not reported** Overall risk of bias: **Moderate and small sample size**

[28] Includes leiomyoma, adenomyosis, pelvic inflammatory disease, mature cystic teratoma, mucinous cystadenoma, or hydrosalpinges.
[29] Dunselman et al. European Society of Human Reproduction and Embryology. ESHRE guideline: management of women with endometriosis. Hum Reprod 2014. 29:400–12.

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 19)
Full citation Baggio et al. 2016. **Country** Italy **Study type** Prospective *See Table 6*	**Population** Patients suspected of deep infiltrating endometriosis enrolled to undergo surgical treatment **Sample size** 92 patients for CA125 *See Table 6*	Index test 1 CA 125 >35 µg/mL Index test 2 TVS (without BP) Index test 3 CTC with BP and iodinated contrast Index test 4 Intestinal symptoms Reference standard Laparoscopic findings and subsequent pathological confirmation	*See Table 6*	****2x2 available**** **CA 125** Sensitivity: 0.59 Specificity: 0.86 *See Table 6*	*See Table 6*	Overall risk of bias assessment: **High and small sample size**

Abbreviations: CA 125, serum Cancer Antigen 125; CPP, chronic pelvic pain; CTC, computed tomography colonography; DIE, deep infiltrating endometriosis; NPV, negative predictive value; PPV, positive predictive value; TVS, transvaginal sonography; VAS, visual analogue scale.

Table 19 QUADAS-2 Diagnostic accuracy checklist: Diagnosis of endometriosis– peripheral biomarkers

Domain	Question	Hirsch 2017	Baggio 2016
Patient selection			
Signalling questions	Was a consecutive or random sample of patients enrolled?	Yes	Unclear (not reported)
	Was a case-control design avoided?	Yes	Yes
	Did the study avoid inappropriate exclusions?	Yes	Unclear (not reported)
Risk of Bias	**Could the selection of patients have introduced bias?**	**Low**	**Unclear**
Concerns regarding applicability	Are there concerns that the included patients and setting do not match the review question?	High (tertiary referral centre – more likely to see complex/severe cases)	Unclear (single centre)
Index Test			
Signalling questions	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	Yes
	If a threshold was used, was it pre-specified?	Yes	Yes
Risk of bias	**Could the conduct or interpretation of the index test have introduced bias?**	**Low**	**Low**
Concerns regarding applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear (level of experience of person interpreting test not reported)	Low
Reference Standard			

Domain	Question	Hirsch 2017	Baggio 2016
Signalling questions	Is the reference standard likely to correctly classify the target condition?	Yes (based on ESHRE guidance)	Unclear (criteria for diagnosis not reported)
	Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes	Unclear (information not reported)
Risk of Bias	**Could the reference standard, its conduct, or its interpretation have introduced bias?**	**Low**	**Unclear**
Concerns regarding applicability	Are there concerns that the target condition as defined by the reference standard does not match the question?	High (not all patients with endometriosis undergo surgery)	High (only DIE and not all patients with endometriosis undergo surgery)
Flow and Timing			
Signalling questions	Was there an appropriate interval between index test and reference standard?	Yes (same day)	Yes (1 week)
	Did all patients receive a reference standard?	Yes	Yes
	Did all patients receive the same reference standard?	Yes	Yes
	Were all patients included in the analysis?	Yes	Yes
Risk of Bias	**Could the patient flow have introduced bias?**	**Low**	**Low**

Abbreviations: DIE, deep infiltrating endometriosis; ESHRE, European Society of Human Reproduction and Embryology.

Surgical diagnosis

No new relevant diagnostic studies were identified.

Evidence summaries

Clinical examination

Table 20 High level summary: Diagnosis of endometriosis – clinical examination

Author Year	Country Setting	No. subjects Recruitment	Inclusion criteria	Method of clinical examination	Cases identified by reference standard	Overall risk of bias	Site(s) of endometriosis evaluated	Sensitivity% (95% CI)	Specificity% (95% CI)
Berger 2019	The Netherlands Single referral centre	72 Prospective	Clinical suspicion of endometriosis	1. History (symptoms of dyspareunia, dysmenorrhoea, dysuria, dyschezia, and cyclic or CPP and subfertility) 2. Physical exam	81.9% DIE	High	1. Endometriosis	61.5	0
							1. DIE	60.0	0
							1. + 2. Endometriosis	58.6	0
							1. + 2. DIE	59.3	0
Chen 2019	China Tertiary referral centre	29 Retrospective	Clinical suspicion of RVE	Digital vaginal and rectovaginal examination (bimanual and trimanual)	72.4% RVE 52.4% other endometriosis	High	Rectovaginal	95.2 (74.1, 99.8)	62.5 (25.9, 89.8)
Baggio 2016	Italy Single centre	92 Prospective	Clinical suspicion of DIE	Detailed history focusing on intestinal symptoms	100% DIE 53.3% bowel endometriosis	High	Bowel involvement	67	56
Hudelist 2011	UK and Austria 3 PP clinics	129 Prospective	Clinical suspicion of endometriosis	Vaginal examination (bimanual)	64% endometriosis 40% DIE	High	Ovary	41 (22, 61)	99 (95, 100)
							Uterosacral ligaments	50 (31, 69)	80 (71, 87)
							Pouch of Douglas	76 (53, 92)	92 (85, 96)
							Vagina	76 (53, 92)	98 (94, 100)
							Rectovaginal space	78 (40, 97)	98 (94, 100)
							Urinary bladder	25 (0, 81)	100 (96, 100)
							Rectosigmoid	39 (22, 58)	97 (93, 100)

Abbreviations: CI, confidence interval; DIE, deep infiltrating endometriosis; PP, pelvic pain; RVE, rectovaginal endometriosis.
Note: For studies shown in grey text, 2x2 data (FP, FN, TP, TN) are not available.

Ultrasound

Transvaginal ultrasound

Table 21 High level summary: Diagnosis of endometriosis – transvaginal ultrasound

Author Year	Country Setting	No. subjects Recruitment	Inclusion criteria	Method of ultrasound	Cases identified by reference standard	Overall risk of bias	Site(s) of endometriosis evaluated	Sensitivity% (95% CI)	Specificity% (95% CI)
Non-enhanced									
Berger 2019	The Netherlands Single referral centre	72 Prospective	Clinical suspicion of endometriosis Physical exam	Dynamic TVS, non-enhanced	81.9% DIE	High	Endometriosis	93.7	55.6
							DIE	93.2	NN
Chen 2019	China Tertiary referral centre	29 Retrospective	Clinical suspicion of RVE	2D-TVS, non-enhanced	72.4% with RVE 52.4% with other endometriosis	High	Rectovaginal	42.9 (22.6, 65.6)	87.5 (46.7, 99.3)
							Rectal infiltration	26.7 (8.9, 55.2)	85.7 (56.2, 97.5)
Ferrero 2019a	Italy Single tertiary referral centre	262 Prospective	Clinical suspicion of endometriosis	1. 2D-TVS, non-enhanced 2. 2D-TVS, non-enhanced (only BP)	45.0% rectosigmoid endometriosis 51.9% endometriosis without rectosigmoid involvement	High	1. Rectosigmoid	88.1 (80.9, 93.4)	95.8 (91.2, 98.5)
							2. Rectosigmoid	90.7 (83.9, 95.3)	95.8 (91.2, 98.5)
Rosefort 2019	France Single centre, hospital	115 Retrospective	Clinical suspicion of DIE	2D-TVS, non-enhanced (trained operator)	86.9% posterior DIE 34% bowel involvement	High	DIE	58 (46, 70)	87.5 (63, 100)
							Rectal DIE	40 (23, 59)	93 (86, 100)
Alborzi 2018	Iran Single tertiary centre	317 Prospective	Clinical suspicion of endometriosis Physical exam	2D-TVS, non-enhanced (only BP)	79.5% with DIE	High	DIE	83.3 (78, 88)	46.1 (34, 59)
							USLs	70.9 (63, 78)	92.8 (88, 96)
							Rectal wall	88.5 (77, 96)	98.9 (97, 100)
							Retrocervical	52.8 (36, 69)	94.6 (91, 97)
							RV septum	86.4 (73, 95)	94.9 (92, 97)
							Ureter	100 (16, 100)	100 (99, 100)
							Ovarian fossa	62.7 (49, 75)	95.7 (92, 98)

Author Year	Country Setting	No. subjects Recruitment	Inclusion criteria	Method of ultrasound	Cases identified by reference standard	Overall risk of bias	Site(s) of endometriosis evaluated	Sensitivity% (95% CI)	Specificity% (95% CI)
							Bladder	100 (40, 100)	99.7 (98, 100)
Reid 2018	Australia 2 tertiary referral PP centres	376 Prospective	Clinical suspicion of endometriosis	1. 2D-TVS, non-enhanced, "sliding sign" 2. 2D-TVS, non-enhanced, "direct visualisation" 3. 2D-TVS, non-enhanced, "combined"	20.2% rectal or rectosigmoid DIE	High	1. Rectal/rectosigmoid	73.7 (62.3, 83.1)	90.3 (86.4, 96.4)
							2. Rectal/rectosigmoid	86.8 (77.1, 93.5)	92.3 (88.7, 95.1)
							3. Rectal/rectosigmoid	69.7 (58.1, 79.8)	95.3 (92.3, 97.4)
Ros 2017	Spain Tertiary university hospital	40 Prospective	Clinical suspicion of DIE Physical exam (some)	1. TVS, non-enhanced 2. TVS, non-enhanced (only BP)	37.5% rectosigmoid involvement	High	1. Rectosigmoid nodules	73	88
							2. Rectosigmoid nodules	100	96
Young 2017	United States Single tertiary referral centre	57 Retrospective	Clinical suspicion of deep endometriosis Physical exam (some)	3D-TVS, non-enhanced (only BP)	40.4% deep endometriosis	High	Rectosigmoid and/or rectovaginal septum	94 (70,100)	100 (91,100)
							Retrocervical and/or uterosacral ligament	86 (65, 97)	94 (81, 99)
Baggio 2016	Italy Single centre	92 Prospective	Clinical suspicion of DIE	2D-TVS[30], non-enhanced	100% DIE 53.3% bowel endometriosis	High	Bowel involvement	41[31]	93[31]
Enhanced									
Ferrero 2019b	Italy Single tertiary referral centre	155 Prospective	Clinical suspicion of DIE Physical exam	1. TVS, enhanced (RWC) 2. TVS, enhanced (RWC, BP)	59.4% rectosigmoid endometriosis	High	1. Rectosigmoid	88.0 (79.6, 93.9)	90.5 (80.4, 96.4)
							2. Rectosigmoid	91.3 (83.6, 91.2)	88.9 (78.4, 95.4)
Ferrero 2017	Italy Single tertiary referral centre	70 Prospective	Clinical suspicion of rectosigmoid endometriosis Clinical exam	TVS, enhanced (RWC, BP)	57.1% rectosigmoid endometriosis	High	Rectosigmoid	92.5 (78.6, 98.4)	96.7 (82.9, 99.9)
							Multifocal rectosigmoid	80.0 (28.4, 99.5)	97.1 (85.1, 99.9)
Jiang 2017	China Hospital ultrasound centre	198 Prospective	Clinical suspicion of bowel endometriosis Clinical exam	TVS, enhanced (RWC)	55.6% bowel endometriosis 14.1% infiltration of intestinal serosa	High	Bowel and rectosigmoid	88.2	97.3
Leone Roberti Maggiore 2017		286 Prospective	Clinical suspicion of rectosigmoid	TVS, enhanced (RWC, BP)	52.8% rectosigmoid endometriosis	High	Rectosigmoid	92.7 (87.3, 96.3)	97.0 (92.6, 99.2)

[30] 4D transabdominal was used in some cases (data not shown separately).
[31] Inconsistently reported in publication.

Author Year	Country Setting	No. subjects Recruitment	Inclusion criteria	Method of ultrasound	Cases identified by reference standard	Overall risk of bias	Site(s) of endometriosis evaluated	Sensitivity% (95% CI)	Specificity% (95% CI)
	Italy Single tertiary centre		endometriosis Physical exam (some)		8.6% infiltration of mucosa		Infiltration of bowel mucosa	76.9 (46.2, 95.0)	86.1 (81.4, 90.0)

Abbreviations: BP, bowel preparation; CI, confidence interval; DIE, deep infiltrating endometriosis; NN, no number; PP, pelvic pain; RVE, rectovaginal endometriosis; RWC, rectal water contrast; TVS, transvaginal ultrasound.
Note: For studies shown in grey text, 2x2 data (FP, FN, TP, TN) are not available.

Transvaginal plus transabdominal ultrasound

Table 22 High level summary: Diagnosis of endometriosis – transvaginal plus transabdominal ultrasound

Author Year	Country Setting	No. subjects Recruitment	Inclusion criteria	Method of ultrasound	Cases identified by reference standard	Overall risk of bias	Site(s) of endometriosis evaluated	Sensitivity% (95% CI)	Specificity% (95% CI)
Hernandez Gutierrez 2019	Spain Single referral centre	48 Retrospective	Clinical suspicion of DIE Physical exam	2D-TVS, non-enhanced (only BP) + transabdominal scan	100% with DIE	High	Rectovaginal space	65	88
							Vagina	67	96
							Uterosacral ligaments	59	43
							Rectosigmoid	81	62
							Bladder	50	98
							Ureter	50	95
Zannoni 2017	Italy Single tertiary centre	47 Prospective	Clinical suspicion of DIE Physical exam	2D-TVS, non-enhanced + transabdominal scan	95.7% with DIE nodule(s) in posterior compartment	High	Intestinal	97.5	33.3
							Right ureteral	10.0	94.8
							Left ureteral	28.5	96.3

Abbreviations: BP, bowel preparation; CI, confidence interval; DIE, deep infiltrating endometriosis; NN, not a number; TVS, transvaginal ultrasound.
Note: For studies shown in grey text, 2x2 data (FP, FN, TP, TN) are not available.

Rectal scanning

Table 23 High level summary: Diagnosis of endometriosis – rectal scanning

Author Year	Country Setting	No. subjects Recruitment	Inclusion criteria	Method of rectal scanning	Cases identified by reference standard	Overall risk of bias	Site(s) of endometriosis evaluated	Sensitivity% (95% CI)	Specificity% (95% CI)
Chen 2019	China Tertiary referral centre	29 Retrospective	Clinical suspicion of RVE	RES, non-enhanced (only BP)	72.4% with RVE 52.4% with other endometriosis	High	RVE	81.0 (57.4, 93.7)	75.0 (35.6, 95.5)
							Rectal infiltration	86.7 (58.4, 97.7)	85.7 (56.2, 97.5)
Alborzi 2018	Iran Single tertiary centre	317 Prospective	Clinical suspicion of endometriosis Physical exam	TRS, non-enhanced (only BP)	79.5% with DIE	High	DIE	80.5	18.6
							USLs	82.8	89.8
							Rectal wall	86.5	97.7
							Retrocervical	50	96.1
							RV septum	84.1	93.8
							Ureter	100	100
							Ovarian fossa	64.4	93.4
							Bladder	100	99.7

Abbreviations: BP, bowel preparation; CI, confidence interval; DIE, deep infiltrating endometriosis; RES, rectal endoscopic sonography; RVE, rectovaginal endometriosis; TRS, transrectal sonography.
Note: For studies shown in grey text, 2x2 data (FP, FN, TP, TN) are not available.

Computed tomography

Table 24 High level summary: Diagnosis of endometriosis – computed tomography

Author Year	Country Setting	No. subjects Recruitment	Inclusion criteria	Method of CT	Cases identified by reference standard	Overall risk of bias	Site(s) of endometriosis evaluated	Sensitivity% (95% CI)	Specificity% (95% CI)
Mehedintu 2018	France Single tertiary referral centre	71 Retrospective	Planned surgery for DIE of rectum or sigmoid	CTC, enhanced (CO_2 distension, contrast)	100% with endometriotic intestinal lesions	High	Rectal nodules	77.1 (64.5, 86.8)	100 (69.2, 100)
							Sigmoid nodules	86.4 (65.1, 97.1)	95.9 (86.0, 99.5)
Ferrero 2017	Italy Single tertiary referral centre	70 Prospective	Clinical suspicion of rectosigmoid endometriosis Clinical exam	16-section CTC (air distension, no contrast)	57.1% rectosigmoid endometriosis	High	Rectosigmoid	92.5 (79.6, 98.4)	86.7 (69.3, 96.2)
							Multifocal rectosigmoid	40.0 (5.3, 85.3)	91.4 (76.9, 98.2)
Zannoni 2017	Italy Single tertiary centre	47 Prospective	Clinical suspicion of DIE Physical exam	64-row CTC (air distension, iodinated contrast)	95.7% with DIE nodule(s) in posterior compartment	High	Intestinal	78.0	50.0
							Right ureteral	60.0	70.2
							Left ureteral	57.1	76.9

Author Year	Country Setting	No. subjects Recruitment	Inclusion criteria	Method of CT	Cases identified by reference standard	Overall risk of bias	Site(s) of endometriosis evaluated	Sensitivity% (95% CI)	Specificity% (95% CI)
Baggio 2016	Italy Single centre	37 Prospective	Clinical suspicion of DIE	64-row CTC (CO_2 distension, iodinated contrast)	100% DIE 53.3% bowel endometriosis	High	Bowel involvement	68	67
Biscaldi 2014	Italy Single referral centre	260 Prospective	Symptoms suggestive of rectosigmoid endometriosis	64-row MDCT (water distension, iodinated contrast)	67.7% rectosigmoid endometriotic nodules	High	Rectosigmoid	98.3	98.8
Iosca 2013	Italy University hospital	64 Retrospective	Suspicion of bowel endometriosis	64-row MSCT (water distension, iodinated contrast)	85.9% endometriotic lesions	High	Bowel	100	97.6
							Ureteral	72.2	100
Stabile Ianora 2013	Italy University hospital	33 Prospective	Clinical suspicion of bowel endometriosis	64-row MSCT (water distension, iodinated contrast)	69% intestinal endometriotic implants	High	Bowel	87	100
Biscaldi 2011	Italy University hospital	103 Prospective	Suspicion of bowel endometriosis	16-row MDCT enteroclysis urography (iodinated contrast)	65.0% bowel endometriotic nodules	High	Bowel nodules	95.5	97.2
							Bowel nodules infiltrating at least the muscular layer	93.3	96.6
							Ureteral compression	97.1	98.8
Ferrero 2011	Italy Single referral centre	96 Prospective	Suspicion of bowel endometriosis	16-row MDCT (enema, iodinated contrast)	53.1% bowel endometriotic nodules	High	Bowel	96.1	100
							Rectosigmoid	95.8	100

Abbreviations: CI, confidence interval; CO_2, carbon dioxide; CTC, computed tomography colonoscopy; DIE, deep infiltrating endometriosis; MDCT, multidetector computerised tomography; MSCT, multislice computed tomography.

Note: For studies shown in grey text, 2x2 data (FP, FN, TP, TN) are not available.

Magnetic resonance imaging

Table 25 High level summary: Diagnosis of endometriosis – magnetic resonance imaging

Author Year	Country Setting	No. subjects Recruitment	Inclusion criteria	Method of MRI	Cases identified by reference standard	Overall risk of bias	Site(s) of endometriosis evaluated	Sensitivity% (95% CI)	Specificity% (95% CI)
Berger 2019	The Netherlands Single referral centre	72 Prospective	Clinical suspicion of endometriosis Clinical exam TVUS	1.5-T MRI (no BP, no contrast)	81.9% DIE	High	Endometriosis	85.9	62.5
							DIE	88.1	NN
Chen 2019	China Tertiary referral centre	29 Retrospective	Clinical suspicion of RVE	3.0-T MRI (gadolinium contrast)	72.4% RVE 52.4% other endometriosis	High	RVE	90.5 (68.2, 98.3)	87.5 (46.7, 99.3)
							Rectal infiltration	73.3 (44.8, 91.1)	92.9 (64.2, 99.6)
Hernandez Gutierrez 2019	Spain Single referral centre	48 Retrospective	Clinical suspicion of DIE Physical exam	1.5-T MRI (ultrasonographic gel distension)	100% with DIE	High	Rectovaginal space	74	64
							Vagina	33	93
							Uterosacral ligaments	67	43
							Rectosigmoid	69	87
							Bladder	67	100
							Ureter	33	98
Alborzi 2018	Iran Single tertiary centre	317 Prospective	Clinical suspicion of endometriosis Physical exam	1.5-T MRI (gadolinium contrast)	79.5% with DIE	High	All DIE lesions	90.4	66.1
							Uterosacral ligaments	63.58	93.98
							Rectal wall	76.92	96.6
							Retrocervical	65.79	96.42
							Rectovaginal septum	72.73	95.24
							Ureter	100	100
							Ovarian fossa	66.1	98.06
							Bladder	100	99.68
Mehedintu 2018	France Single tertiary referral centre	71 Retrospective	Planned surgery for DIE of rectum or sigmoid	1.5-T MRI (ultrasonographic gel)	100% with endometriotic intestinal lesions	High	Rectal nodules	83.6 (71.9, 91.8)	90 (55.5, 99.7)
							Sigmoid nodules	54.6 (32.2, 75.6)	93.9 (83.1, 98.7)
Yap 2018	Australia Tertiary women's hospital	37 Retrospective	Clinical suspicion of endometriosis	3-T MRI (no patient prep, no contrast)	Unclear	High	Any endometriosis	76.9 (69.7, 84.0)	98.5 (97.3, 99.6)
							Anterior compartment	33 (0, 86.7)	100 (100, 100)

Author Year	Country Setting	No. subjects Recruitment	Inclusion criteria	Method of MRI	Cases identified by reference standard	Overall risk of bias	Site(s) of endometriosis evaluated	Sensitivity% (95% CI)	Specificity% (95% CI)
							Posterior compartment	76.5 (66.4, 86.6)	99.4 (98.1, 100)
							Middle compartment	79.4 (69.4, 89.4)	95.1 (91.2, 98.9)
							Rectosigmoid	94.4 (83.9, 100)	94.7 (84.7, 100)
							Right ovary	100 (100, 100)	85.0 (69.4, 100)
							Left ovary	93.8 (81.9, 100)	95.2 (86.1, 100)
							Uterus	86.7 (69.5, 100)	100 (100, 100)
Leone Roberti Maggiore 2017	Italy Single tertiary centre	286 Prospective	Clinical suspicion of rectosigmoid endometriosis Physical exam (some)	1.5-T MR-e (ultrasonographic gel distension)	52.8% rectosigmoid endometriosis 8.6% infiltration of mucosa	High	Rectosigmoid	95.4 (90.7, 99.1)	97.8 (93.6, 99.5)
							Infiltration of mucosal layer of bowel wall	66.7 (34.9, 90.1)	85.0 (80.3, 89.0)
Biscaldi 2014	Italy Single referral centre	260 Prospective	Symptoms suggestive of rectosigmoid endometriosis	1.5-T MRI (ultrasonographic gel distension)	67.7% rectosigmoid endometriotic nodules	High	Rectosigmoid	97.2	96.4

Abbreviations: BP, bowel preparation; CI, confidence interval; DIE, deep infiltrating endometriosis; MDCT, multidetector computerised tomography; MRI-e, magnetic resonance imaging with enema; MRI, magnetic resonance imaging; RVE, retrovaginal endometriosis; TVUS, transvaginal utrasonography.
Note: For studies shown in grey text, 2x2 data (FP, FN, TP, TN) are not available.

Biomarkers

Table 26 High level summary: Diagnosis of endometriosis – biomarkers

Author Year	Country Setting	No. subjects Recruitment	Inclusion criteria	Method of biomarker testing	Cases identified by reference standard	Overall risk of bias	Site(s) of endometriosis evaluated	Sensitivity% (95% CI)	Specificity% (95% CI)
Hirsch 2017	United Kingdom 2 tertiary referral hospitals	58 Prospective	Suspicion of endometriosis	Serum CA 125 >30 µ/mL, immunoassay	51.7% confirmed endometriosis	Moderate	Endometriosis	57 (37.4, 74.5)	96 (81.7, 99.9)
Baggio 2016	Italy Single centre	92 Prospective	Clinical suspicion of DIE	Serum CA 125 >35 µg/mL	100% DIE 53.3% bowel endometriosis	High	Bowel endometriosis	59	86

Abbreviations: CA, cancer antigen; CI, confidence interval; DIE, deep infiltrating endometriosis.
Note: For studies shown in grey text, 2x2 data (FP, FN, TP, TN) are not available.

Surgical diagnosis

No new relevant diagnostic studies were identified.

Summary of direct comparisons of different diagnostic modalities

Table 27 High level summary: Diagnosis of endometriosis – studies directly comparing different diagnostic modalities for endometriosis

Author, year	Country N	Site	Sensitivity % (95% CI)					Specificity % (95% CI)				
			Clinical exam	TVS	TRUS	CT	MRI	Clinical exam	TVS	TRUS	CT	MRI
Berger 2019 *Prospective*	The Netherlands 72	Endometriosis	58.6	93.7			85.9	0	55.6			62.5
		DIE	59.3	93.2			88.1	0	NN			NN
Chen 2019 *Retrospective*	China 29	Rectovaginal	95.2 (74.1, 99.8)	42.9 (22.6, 65.6)	81.0 (57.4, 93.7)		90.5 (68.2, 98.3)	62.5 (25.9, 89.8)	87.5 (46.7, 99.3)	75.0 (35.6, 95.5)		87.5 (46.7, 99.3)
		Rectal infiltration		26.7 (8.9, 55.2)	86.7 (58.4, 97.7)		73.3 (44.8, 91.1)		85.7 (56.2, 97.5)	85.7 (56.2, 97.5)		92.9 (64.2, 99.6)
Hernandez Gutierrez 2019 *Retrospective*	Spain 48	Rectovaginal		65			74		88			64
		Vagina		67			33		96			93
		USLs		59			67		43			43
		Rectosigmoid		81			69		62			87
		Bladder		50			67		98			100
		Ureter		50			33		95			98
Alborzi 2018 *Prospective*	Iran 317	DIE		83.3	80.5		90.4		46.1	18.6		66.1
		USLs		70.9	82.8		63.6		92.8	89.8		94.0
		Rectal wall		88.5	86.5		76.9		98.9	97.7		96.6
		Ovarian fossa		62.7	64.4		66.1		95.7	93.4		98.1
		Retrocervical		52.8	50		65.8		94.6	96.1		96.4
		RV septum		86.4	84.1		72.7		94.9	93.8		95.2
		Bladder		100	100		100		99.7	99.7		99.7
		Ureter		100	100		100		100	100		100
Mehedintu 2018 *Retrospective*	France 71	Rectal nodules				77.1 (64.5, 86.8)	83.6 (71.9, 91.8)				100 (69.2, 100)	90 (55.5, 99.7)
		Sigmoid nodules				86.4 (65.1, 97.1)	54.6 (32.2, 75.6)				95.9 (86.0, 99.5)	93.9 (83.1, 98.7)

Author, year	Country N	Site	Sensitivity % (95% CI)					Specificity % (95% CI)				
			Clinical exam	TVS	TRUS	CT	MRI	Clinical exam	TVS	TRUS	CT	MRI
Ferrero 2017 *Prospective*	Italy 70	Rectosigmoid		92.5[32] (78.6, 98.4)		92.5 (79.6, 98.4)			96.7[32] (82.9, 99.9)		86.7 (69.3, 96.2)	
		Multifocal rectosigmoid		80.0[32] (28.4, 99.5)		40.0 (5.3, 85.3)			97.1[32] (85.1, 99.9)		91.4 (76.9, 98.2)	
Leone Roberti Maggiore 2017 *Prospective*	Italy 286	Rectosigmoid		92.7[32] (87.3, 96.3)			95.4 (90.7, 99.1)		97.0[32] (92.6, 99.2)			97.8 (93.6, 99.5)
		Infiltration of bowel mucosa		76.9 (46.2, 95.0)			66.7 (34.9, 90.1)		86.1 (81.4, 90.0)			85.0 (80.3, 89.0)
Zannoni 2017 *Prospective*	Italy 47	Intestinal		97.5[33]		78.0			33.3[33]		50.0	
		Right ureteral		10.0[33]		60.0			94.8[33]		70.2	
		Left ureteral		28.5[33]		57.1			96.3[33]		76.9	
Baggio 2016 *Prospective*	Italy 92 (37 CT)	Bowel	67	41		68		56	93		67	
Biscaldi 2014 *Prospective*	Italy 260	Rectosigmoid				98.3	97.2				98.8	96.4
Ferrero 2011 *Prospective*	Italy 96	Bowel		99.2		96.1			97.8		100	
		Rectosigmoid		93.8		95.8			97.9		100	
Hudelist 2011 *Prospective*	UK and Austria 129	Ovary	41 (22,61)	96 (81, 100)				99 (95, 100)	96 (90, 99)			
		USLs	50 (31, 69)	63 (44, 80)				80 (71, 87)	98 (93, 100)			
		Pouch of Douglas	76 (53, 92)	76 (53, 92)				92 (85, 96)	100 (95, 100)			
		Vagina	73 (39, 94)	64 (31, 89)				98 (94, 100)	99 (95, 100)			
		RV space	78 (40, 97)	78 (40, 97)				98 (94, 100)	100 (96, 100)			
		Bladder	25 (0, 81)	50 (7, 93)				100 (96, 100)	98 (94, 100)			
		Rectosigmoid	39 (22, 58)	90 (74, 98)				97 (93, 100)	99 (94, 100)			

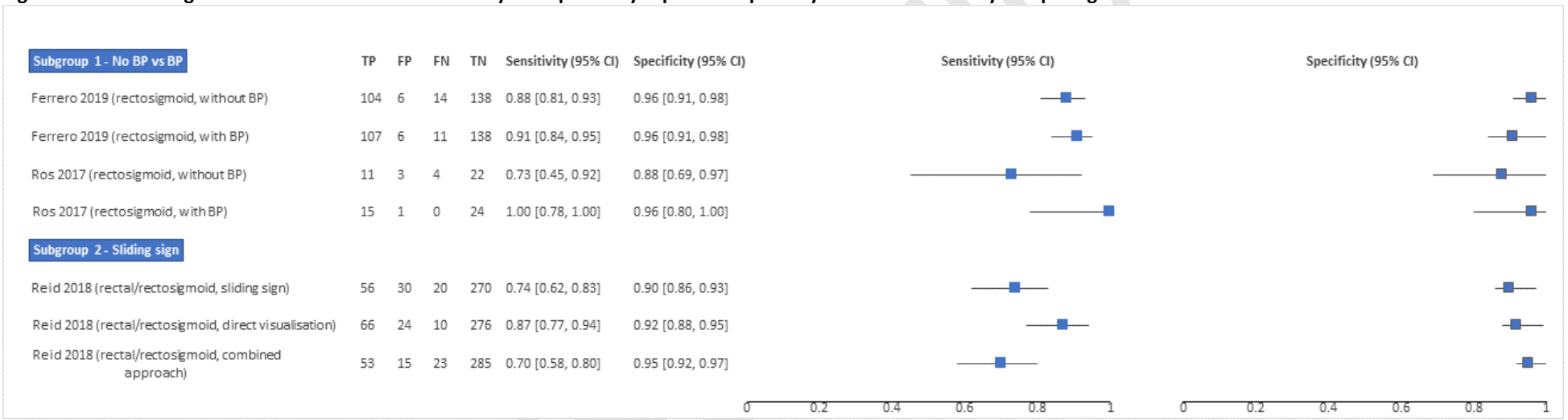
[32] Rectal water contrast TVS
[33] Transvaginal plus transabdominal scan

Abbreviations: CI, confidence interval; CT, computed tomography; DIE, deep infiltrating endometriosis; MRI, magnetic resonance imaging; NN, not a number; RV, rectovaginal; TRUS, transrectal ultrasonography; TVS, transvaginal sonography; USLs, uterosacral ligaments.
Note: For studies shown in grey text, 2x2 data (FP, FN, TP, TN) are not available.

Forest plots

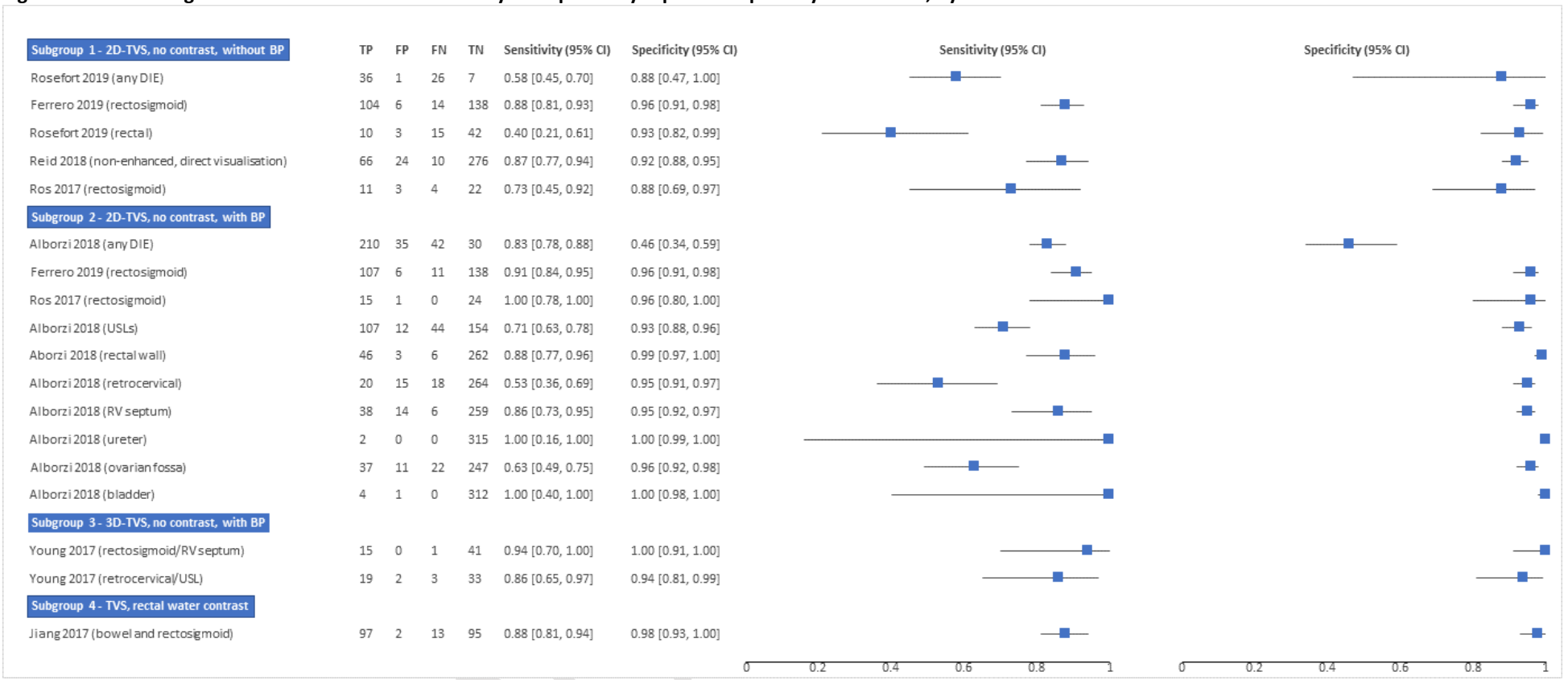
Ultrasound

Figure 2 Diagnosis of endometriosis – sensitivity and specificity reported in primary TVS studies directly comparing different methods



Abbreviations: BP, bowel preparation; CI, confidence interval; FN, false negative; FP, false positive; TN, true negative; TP, true positive.

Figure 3 Diagnosis of endometriosis – sensitivity and specificity reported in primary TVS studies, by site and ultrasound method



Abbreviations: 2D, two-dimensional; 3D, three-dimensional; BP, bowel preparation; CI, confidence interval; DIE, deep infiltrating endometriosis; FN, false negative; FP, false positive; RV, rectovaginal; TN, true negative; TP, true positive; TVS, transvaginal sonography; USLs, uterosacral ligaments.

Clinical evidence profile

Evidence profiles were only developed for the studies that provided sufficient information to construct 2x2 tables.

Clinical examination

Table 28 Evidence Profile Table: Diagnosis of endometriosis – clinical examination

Index test	Site evaluated	No. of studies *References*	No. of participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95% CI)	Specificity (95% CI)	Quality of the evidence (GRADE)
Detailed history focusing on intestinal symptoms	Bowel	1 *Baggio et al 2016*	92	High[1]	N/A	Serious indirectness[3]	Serious imprecision[5]	67	56	Very low
Vaginal examination (bimanual)	Ovary	1 *Hudelist 2011*	129	High[2]	N/A	Serious indirectness[4]	Serious imprecision[6]	41 (22, 61)	99 (95, 100)	Very low
	Uterosacral ligaments	1 *Hudelist 2011*	129	High[2]	N/A	Serious indirectness[4]	Serious imprecision[6]	50 (31, 69)	80 (71, 87)	Very low
	Pouch of Douglas	1 *Hudelist 2011*	129	High[2]	N/A	Serious indirectness[4]	Serious imprecision[6]	76 (53, 92)	92 (85, 96)	Very low
	Vagina	1 *Hudelist 2011*	129	High[2]	N/A	Serious indirectness[4]	Serious imprecision[6]	76 (53, 92)	98 (94, 100)	Very low
	Rectovaginal space	1 *Hudelist 2011*	129	High[2]	N/A	Serious indirectness[4]	Serious imprecision[6]	78 (40, 97)	98 (94, 100)	Very low
	Urinary bladder	1 *Hudelist 2011*	129	High[2]	N/A	Serious indirectness[4]	Very serious imprecision[6]	25 (0, 81)	100 (96, 100)	Very low
	Rectosigmoid	1 *Hudelist 2011*	129	High[2]	N/A	Serious indirectness[4]	Serious imprecision[6]	39 (22, 58)	97 (93, 100)	Very low

Abbreviations: CI, confidence interval; N/A, not applicable.

1. Unclear if study used a consecutive or random sample; unclear if exclusions were appropriate, not all women received the same reference standard.
2. Unclear if study used a consecutive or random sample; unclear if there's an appropriate time frame between index and reference test.
3. DIE patients who undergo surgery may have a different profile to those who do not undergo surgery, and those who do not have DIE; single centre. Unclear if intestinal symptoms is representative of clinical exam.
4. Endometriosis patients who undergo surgery may have a different profile to those who do not. Unclear if vaginal exam is representative of clinical exam in practice.
5. Confidence interval and variance not reported.
6. Large confidence interval (for sensitivity).

Transvaginal ultrasound

Table 29 Evidence Profile Table: Diagnosis of endometriosis – ultrasound

Index test	Site evaluated	No. of studies *References*	No. of participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95% CI)	Specificity (95% CI)	Quality of the evidence (GRADE)
2D TVS non-enhanced										
2D-TVS, non-enhanced	Rectosigmoid	1 *Ferrero et al 2019a*	262	High[1]	N/A	High[8]	No serious imprecision	88.1 (80.9, 93.4)	95.8 (91.2, 98.5)	Very low
2D-TVS, non-enhanced (only BP)	Rectosigmoid	1 *Ferrero et al 2019a*	262	High[1]	N/A	High[8]	No serious imprecision	90.7 (83.9, 95.3)	95.8 (91.2, 98.5)	Very low
2D-TVS, non-enhanced (trained operator)	DIE	1 *Rosefort et al 2019*	115	High[2]	N/A	High[9]	Serious imprecision[12]	58 (46, 70)	87.5 (63, 100)	Very low
2D-TVS, non-enhanced (trained operator)	Rectal DIE	1 *Rosefort et al 2019*	115	High[2]	N/A	High[9]	Serious imprecision[12]	40 (23, 59)	93 (86, 100)	Very low
2D-TVS, non-enhanced (only BP)	DIE	1 *Alborzi et al 2018*	317	High[3]	N/A	High[9]	No serious imprecision	83.3 (78, 88)	46.1 (34, 59)	Very low
	USLs	1 *Alborzi et al 2018*	317	High[3]	N/A	High[9]	No serious imprecision	70.9 (63, 78)	92.8 (88, 96)	Very low
	Rectal wall	1 *Alborzi et al 2018*	317	High[3]	N/A	High[9]	No serious imprecision	88.5 (77, 96)	98.9 (97, 100)	Very low
	Retrocervical	1 *Alborzi et al 2018*	317	High[3]	N/A	High[9]	No serious imprecision	52.8 (36, 69)	94.6 (91, 97)	Very low
	RV septum	1 *Alborzi et al 2018*	317	High[3]	N/A	High[9]	No serious imprecision	86.4 (73, 95)	94.9 (92, 97)	Very low
	Ureter	1 *Alborzi et al 2018*	317	High[3]	N/A	High[9]	Very serious imprecision[12]	100 (16, 100)	100 (99, 100)	Very low
	Ovarian fossa	1 *Alborzi et al 2018*	317	High[3]	N/A	High[9]	No serious imprecision	62.7 (49, 75)	95.7 (92, 98)	Very low
	Bladder	1 *Alborzi et al 2018*	317	High[3]	N/A	High[9]	Serious imprecision[12]	100 (40, 100)	99.7 (98, 100)	Very low
2D-TVS, non-enhanced, "sliding sign"	Rectal/rectosigmoid	1 *Reid et al 2018*	376	High[4]	N/A	High[10]	No serious imprecision	73.7 (62.3, 83.1)	90.3 (86.4, 96.4)	Very low
2D-TVS, non-enhanced, "direct visualisation"	Rectal/rectosigmoid	1 *Reid et al 2018*	376	High[4]	N/A	High[10]	No serious imprecision	86.8 (77.1, 93.5)	92.3 (88.7, 95.1)	Very low
2D-TVS, non-enhanced, "combined"	Rectal/rectosigmoid	1 *Reid et al 2018*	376	High[4]	N/A	High[10]	No serious imprecision	69.7 (58.1, 79.8)	95.3 (92.3, 97.4)	Very low

Index test	Site evaluated	No. of studies *References*	No. of participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95% CI)	Specificity (95% CI)	Quality of the evidence (GRADE)
3D TVS non-enhanced										
3D-TVS, non-enhanced (only BP)	Rectosigmoid and/or rectovaginal septum	1 *Young et al 2017*	57	High[6]	N/A	High[9]	No serious imprecision	94 (70,100)	100 (91,100)	Very low
	Retrocervical and/or uterosacral ligament	1 *Young et al 2017*	57	High[6]	N/A	High[9]	No serious imprecision	86 (65, 97)	94 (81, 99)	Very low
TV non-enhanced										
TVS, non-enhanced	Rectosigmoid nodules	1 *Ros et al 2017*	40	High[5]	N/A	High[9]	Serious imprecision[13]	73	88	Very low
TVS, non-enhanced (only BP)	Rectosigmoid nodules	1 *Ros et al 2017*	40	High[5]	N/A	High[9]	Serious imprecision[13]	100	96	Very low
TVS enhanced										
TVS, enhanced (RWC)	Bowel and rectosigmoid	1 *Jiang et al 2017*	198	High[7]	N/A	High[11]	Serious imprecision[13]	88.2	97.3	Very low

Abbreviations: BP, bowel preparation; CI, confidence interval; DIE, deep infiltrating endometriosis; RV, rectovaginal; RWC, rectal water contrast; TVS, transvaginal ultrasound; USL, uterosacral Ligament.

1. Reference standard results were not interpreted without knowledge of the results of index test and applicability concerns

2.Large myomas are an inappropriate exclusion, single centre study, some patients had multiple TVUS, reference standard results were not interpreted without knowledge of the results of the index test, unclear if there was an appropriate interval between index test and reference standard and if all patients received the same reference standard.

3.Single centre study, surgeons aware of TVS findings but histologists blinded, interval between index test and reference standard not reported.

4.Exclusion criteria not reported, referral centre likely to see more severe cases, surgeons aware of imaging findings; unclear if histologists blinded, unclear if all patients received the same reference standard.

5. Surgeons aware of imaging findings; unclear if histologists blinded, unclear is BP protocol is standard.

6. Excluded inadequate BP – unclear if this is appropriate, not reported if reference standard results were interpreted without knowledge of index test results or interval between the two.

7.Unclear if consecutive sample used, surgeons aware of imaging findings; unclear if histologists blinded.

8. Not all cases undergo surgery; referral centre more likely to see complex/ severe cases; BP protocol more extensive than in practice; single centre.

9. Not all patients will undergo surgery.

10. Not all cases undergo surgery; referral centre more likely to see complex/ severe cases

11. Not all patients will undergo surgery and conducted in China.

12. Large confidence interval (for sensitivity).

13. Confidence interval not reported.

Rectal scanning

Table 30 Evidence Profile Table: Diagnosis of endometriosis – rectal scanning

Index test	Site evaluated	No. of studies *References*	No. of participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity	Specificity	Quality of the evidence (GRADE)
TRS, non-enhanced (only BP)	DIE	1 *Alborzi et al 2018*	317	High[1]	N/A	Serious indirectness[2]	Serious imprecision[3]	80.5	18.6	Very low

Index test	Site evaluated	No. of studies *References*	No. of participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity	Specificity	Quality of the evidence (GRADE)
	USLs	1 *Alborzi et al 2018*	317	High[1]	N/A	Serious indirectness[2]	Serious imprecision[3]	82.8	89.8	Very low
	Rectal wall	1 *Alborzi et al 2018*	317	High[1]	N/A	Serious indirectness[2]	Serious imprecision[3]	86.5	97.7	Very low
	Retrocervical	1 *Alborzi et al 2018*	317	High[1]	N/A	Serious indirectness[2]	Serious imprecision[3]	50	96.1	Very low
	RV septum	1 *Alborzi et al 2018*	317	High[1]	N/A	Serious indirectness[2]	Serious imprecision[3]	84.1	93.8	Very low
	Ureter	1 *Alborzi et al 2018*	317	High[1]	N/A	Serious indirectness[2]	Serious imprecision[3]	100	100	Very low
	Ovarian fossa	1 *Alborzi et al 2018*	317	High[1]	N/A	Serious indirectness[2]	Serious imprecision[3]	64.4	93.4	Very low
	Bladder	1 *Alborzi et al 2018*	317	High[1]	N/A	H Serious indirectness[2]	Serious imprecision[3]	100	99.7	Very low

Abbreviations: DIE, deep infiltrating endometriosis; N/A, not assessable; TRS; trans rectal scanning; RV, rectovaginal; USL, uterosacral Ligament.

1. Single centre study, surgeons aware of TRS findings but histologists blinded, interval between index test and reference standard not reported.
2. Not all patients undergo surgery.
3. Confidence interval not reported.

Computed tomography

Table 31 Evidence Profile Table: Diagnosis of endometriosis – Computed tomography

Index test	Site evaluated	No. of studies *References*	No. of participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity	Specificity	Quality of the evidence (GRADE)
64-row CTC (CO_2 distension, iodinated contrast)	Bowel involvement	1 *Baggio et al 2016*	37	High[1]	N/A	Serious indirectness[6]	Serious imprecision[9]	68	67	Very low
64-row MSCT (water distension, iodinated contrast)	Bowel	1 *Iosca et al 2013*	64	High[2]	No serious inconsistency	Serious indirectness[7]	Serious imprecision[9]	100	97.6	Very low
		1 *Stabile Ianora et al 2013*	33	High[3]	No serious inconsistency	Serious indirectness[7]	Serious imprecision[9]	87	100	Very low
	Ureteral	1 *Iosca et al 2013*	64	High[2]	N/A	Serious indirectness[7]	Serious imprecision[9]	72.2	100	Very low
16-row MDCT enteroclysis urography (iodinated contrast)	Bowel nodules	1 *Biscaldi et al 2011*	103	High[4]	N/A	Serious indirectness[8]	Serious imprecision[9]	95.5	97.2	Very low
	Bowel nodules infiltrating at least the muscular layer	1 *Biscaldi et al 2011*	103	High[4]	N/A	Serious indirectness[8]	Serious imprecision[9]	93.3	96.6	Very low
	Ureteral compression	1 *Biscaldi et al 2011*	103	High[4]	N/A	Serious indirectness[8]	Serious imprecision[9]	97.1	98.8	Very low
16-row MDCT (enema, iodinated contrast)	Bowel	1 *Ferrero et al 2011*	96	High[5]	N/A	Serious indirectness[7]	Serious imprecision[9]	96.1	100	Very low
	Rectosigmoid	1 *Ferrero et al 2011*	96	High[5]	N/A	Serious indirectness[7]	Serious imprecision[9]	95.8	100	Very low

Abbreviations: CI, confidence interval; CO_2, carbon dioxide; CTC, computed tomography colonoscopy; DIE, deep infiltrating endometriosis; MDCT, multidetector computerised tomography; MSCT, multislice computed tomography; N/A, not assessable.

1. Unclear if study used a consecutive or random sample; unclear if exclusions were appropriate, not all women received the same reference standard.
2. Unclear if study used a consecutive or random sample; unclear if exclusions were appropriate, very experienced technicians/clinicians performing the tests, criteria for diagnosis not reported, unclear if reference standard results were interpreted without knowledge of index test results, timeframe not reported.
3. Very experienced technicians/clinicians performing the tests, unclear if reference standard results were interpreted without knowledge of index test results.
4. Unclear if study used a consecutive or random sample, very experienced technicians/clinicians performing the tests, reference standard results were interpreted with knowledge of the results of the index tests.
5. Unclear if study used a consecutive or random sample, very experienced technicians/clinicians performing the tests, unclear if reference standard results were interpreted without knowledge of index test results.
6. DIE patients who undergo surgery may have a different profile to those who do not undergo surgery, and those who do not have DIE; single centre
7. Not all patients undergo surgery.
8. Not all patients with rectosigmoid endometriosis undergo surgery; referral centre therefore more likely to see complex/ severe cases; single centre.
9. No confidence interval reported.

MRI

Table 32 Evidence Profile Table: Diagnosis of endometriosis – MRI

Index test	Site evaluated	No. of studies *References*	No. of participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95% CI)	Specificity (95% CI)	Quality of the evidence (GRADE)
1.5-T MRI (gadolinium contrast)	All DIE lesions	1 *Alborzi et al 2018*	317	High[1]	N/A	Serious indirectness[3]	Serious imprecision[5]	90.4	66.1	Very low
	Uterosacral ligaments	1 *Alborzi et al 2018*	317	High[1]	N/A	Serious indirectness[3]	Serious imprecision[5]	63.58	93.98	Very low
	Rectal wall	1 *Alborzi et al 2018*	317	High[1]	N/A	Serious indirectness[3]	Serious imprecision[5]	76.92	96.6	Very low
	Retrocervical	1 *Alborzi et al 2018*	317	High[1]	N/A	Serious indirectness[3]	Serious imprecision[5]	65.79	96.42	Very low
	Rectovaginal septum	1 *Alborzi et al 2018*	317	High[1]	N/A	Serious indirectness[3]	Serious imprecision[5]	72.73	95.24	Very low
	Ureter	1 *Alborzi et al 2018*	317	High[1]	N/A	Serious indirectness[3]	Serious imprecision[5]	100	100	Very low
	Ovarian fossa	1 *Alborzi et al 2018*	317	High[1]	N/A	Serious indirectness[3]	Serious imprecision[5]	66.1	98.06	Very low
	Bladder	1 *Alborzi et al 2018*	317	High[1]	N/A	Serious indirectness[3]	Serious imprecision[5]	100	99.68	Very low
3-T MRI (no patient prep, no contrast)	Any endometriosis	1 *Yap et al 2018*	37	High[2]	N/A	Serious indirectness[4]	No serious imprecision	76.9 (69.7, 84.0)	98.5 (97.3, 99.6)	Very low
	Anterior compartment	1 *Yap et al 2018*	37	High[2]	N/A	Serious indirectness[4]	Very serious imprecision[6]	33 (0, 86.7)	100 (100, 100)	Very low
	Posterior compartment	1 *Yap et al 2018*	37	High[2]	N/A	Serious indirectness[4]	No serious imprecision	76.5 (66.4, 86.6)	99.4 (98.1, 100)	Very low
	Middle compartment	1 *Yap et al 2018*	37	High[2]	N/A	Serious indirectness[4]	No serious imprecision	79.4 (69.4, 89.4)	95.1 (91.2, 98.9)	Very low
	Rectosigmoid	1 *Yap et al 2018*	37	High[2]	N/A	Serious indirectness[4]	No serious imprecision	94.4 (83.9, 100)	94.7 (84.7, 100)	Very low
	Right ovary	1 *Yap et al 2018*	37	High[2]	N/A	Serious indirectness[4]	No serious imprecision	100 (100, 100)	85.0 (69.4, 100)	Very low

Index test	Site evaluated	No. of studies *References*	No. of participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95% CI)	Specificity (95% CI)	Quality of the evidence (GRADE)
	Left ovary	1 *Yap et al 2018*	37	High[2]	N/A	Serious indirectness[4]	No serious imprecision	93.8 (81.9, 100)	95.2 (86.1, 100)	Very low
	Uterus	1 *Yap et al 2018*	37	High[2]	N/A	Serious indirectness[4]	No serious imprecision	86.7 (69.5, 100)	100 (100, 100)	Very low

Abbreviations: BP, bowel preparation; CI, confidence interval; DIE, deep infiltrating endometriosis; MDCT, multidetector computerised tomography; MRI-e, magnetic resonance imaging with enema; MRI, magnetic resonance imaging.

1. Single centre study, surgeons not blinded to results, interval between index test and reference standard not reported.
2. Unclear if a consecutive or random sample of patients was used, exclusions not reported, reference standard results were interpreted with knowledge of index test results, unclear if there was an appropriate time interval between index test and reference standard
3. Not all patients will undergo surgery.
4. Tertiary referral centre more likely to see complex/ severe cases; single centre and not all patients undergo surgery.
5. No confidence interval reported.
6. Large confidence interval (for sensitivity).

Biomarkers

Table 33 Evidence Profile Table: Diagnosis of endometriosis – Biomarkers

Index test	Site evaluated	No. of studies *References*	No. of participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95% CI)	Specificity (95% CI)	Quality of the evidence (GRADE)
Serum CA 125 >35 µg/mL	Bowel involvement	1 *Baggio et al 2016*	92	High[1]	N/A	Serious indirectness[2]	Serious imprecision[3]	59	86	Very low

Abbreviations: CA, cancer antigen; N/A, not assessable.

1. Unclear if study used a consecutive or random sample; unclear if exclusions were appropriate, not all women received the same reference standard.
2. DIE patients who undergo surgery may have a different profile to those who do not undergo surgery, and those who do not have DIE; single centre.
3. Confidence interval not reported.

Clinical evidence statements

Evidence statements were only developed for the studies that provided sufficient information to construct 2x2 tables.

Clinical examination

Detailed history focusing on intestinal symptoms

Baggio et al 2016 (Italy) – Overall high risk of bias

Bowel involvement

Very low-quality evidence from one study (n=92) found the sensitivity and specificity of clinical examination (detailed history focusing on intestinal symptoms) was 67% and 56% in diagnosing bowel endometriosis.

Vaginal examination (Bimanual)

Hudelist et al 2011 (UK and Austria) – Overall high risk of bias

Ovary

Very low-quality evidence from one study (n=129) found the sensitivity and specificity of vaginal examination was 41% (22, 61) and 99% (95, 100) in diagnosing endometriosis in the ovaries.

Uterosacral ligaments

Very low-quality evidence from one study (n=129) found the sensitivity and specificity of vaginal examination was 50% (31, 69) and 80% (71, 87) in diagnosing endometriosis in the uterosacral ligaments.

Pouch of Douglas

Very low-quality evidence from one study (n=129) found the sensitivity and specificity of vaginal examination was 76% (53, 92) and 92% (85, 96) in diagnosing endometriosis in the uterosacral ligaments.

Vagina

Very low-quality evidence from one study (n=129) found the sensitivity and specificity of vaginal examination was 76% (53, 92) and 98% (94, 100) in diagnosing endometriosis in the vagina.

Rectovaginal space

Very low-quality evidence from one study (n=129) found the sensitivity and specificity of vaginal examination was 78% (40, 97) and 98% (94, 100) in diagnosing endometriosis in the rectovaginal space.

Urinary bladder

Very low-quality evidence from one study (n=129) found the sensitivity and specificity of vaginal examination was 25% (0, 81) and 100% (96, 100) in diagnosing endometriosis in the urinary bladder.

Rectosigmoid

Very low-quality evidence from one study (n=129) found the sensitivity and specificity of vaginal examination was 39% (22, 58) and 97% (93, 100) in diagnosing endometriosis in the urinary bladder.

Transvaginal ultrasound

2D-TVS, non-enhanced

Ferrero et al 2019a (Italy) – Overall high risk of bias

Rectosigmoid

Very low-quality evidence from one study (n=262) found the sensitivity and specificity of 2D-TVS (non-enhanced) was 88.1% (80.9, 93.4) and 95.8% (91.2, 98.5) in diagnosing endometriosis in the rectosigmoid.

2D-TVS, non-enhanced (only BP)

Ferrero et al 2019a (Italy) – Overall high risk of bias

Rectosigmoid

Very low-quality evidence from one study (n=262) found the sensitivity and specificity of 2D-TVS (non-enhanced, only BP) was 90.7% (83.9, 95.3) and 95.8% (91.2, 98.5) in diagnosing rectosigmoid endometriosis.

Alborzi et al 2019a (Iran) – Overall high risk of bias

DIE

Very low-quality evidence from one study (n=317) found the sensitivity and specificity of 2D-TVS (non-enhanced, only BP) was 83.3% (78, 88) and 46.1% (34, 59) in diagnosing DIE.

USLs

Very low-quality evidence from one study (n=317) found the sensitivity and specificity of 2D-TVS (non-enhanced, only BP) was 70.9% (63, 78) and 92.8% (88, 96) in diagnosing endometriosis in the USLs.

Rectal wall

Very low-quality evidence from one study (n=317) found the sensitivity and specificity of 2D-TVS (non-enhanced, only BP) was 88.5% (77, 96) and 98.9% (97, 100) in diagnosing rectal wall endometriosis.

Retrocervical

Very low-quality evidence from one study (n=317) found the sensitivity and specificity of 2D-TVS (non-enhanced, only BP) was 52.8% (36, 69) and 94.6% (91, 97) in diagnosing retrocervical endometriosis.

RV septum

Very low-quality evidence from one study (n=317) found the sensitivity and specificity of 2D-TVS (non-enhanced, only BP) was 86.4% (73, 95) and 94.9% (92, 97) in diagnosing RV septum endometriosis.

Ureter

Very low-quality evidence from one study (n=317) found the sensitivity and specificity of 2D-TVS (non-enhanced, only BP) was 100% (16, 100) and 100% (99, 100) in diagnosing ureter endometriosis.

Ovarian fossa

Very low-quality evidence from one study (n=317) found the sensitivity and specificity of 2D-TVS (non-enhanced, only BP) was 62.7% (49, 75) and 95.7% (92, 98) in diagnosing ovarian fossa endometriosis.

Bladder

Very low-quality evidence from one study (n=317) found the sensitivity and specificity of 2D-TVS (non-enhanced, only BP) was 100% (40, 100) and 99.7% (98, 100) in diagnosing bladder endometriosis.

2D-TVS, non-enhanced (trained operator)

Rosefort et al 2019 (France) – Overall high risk of bias

DIE

Very low-quality evidence from one study (n=115) found the sensitivity and specificity of 2D-TVS (non-enhanced, trained operator) was 58% (46, 70) and 87.5% (63, 100) in diagnosing DIE.

Rectal DIE

Very low-quality evidence from one study (n=115) found the sensitivity and specificity of 2D-TVS (non-enhanced, trained operator) was 40% (23, 59) and 93% (86, 100) in diagnosing rectal DIE.

2D-TVS, non-enhanced, "sliding sign"

Reid et al 2018 (Australia) – Overall high risk of bias

Rectal/rectosigmoid

Very low-quality evidence from one study (n=376) found the sensitivity and specificity of 2D-TVS (non-enhanced, "sliding sign") was 73.7% (62.3, 83.1) and 90.3% (86.4, 96.4) in diagnosing rectal/rectosigmoid endometriosis

2D-TVS, non-enhanced, "direct visualisation"

Reid et al 2018 (Australia) – Overall high risk of bias

Rectal/rectosigmoid

Very low-quality evidence from one study (n=376) found the sensitivity and specificity of 2D-TVS (non-enhanced, "direct visualisation") was 86.8% (77.1, 93.5) and 92.3% (88.7, 95.1) in diagnosing rectal/rectosigmoid endometriosis

2D-TVS, non-enhanced, "combined"

Reid et al 2018 (Australia) – Overall high risk of bias

Rectal/rectosigmoid

Very low-quality evidence from one study (n=376) found the sensitivity and specificity of 2D-TVS (non-enhanced, "combined") was 69.7% (58.1, 79.8) and 95.3% (92.3, 97.4) in diagnosing rectal/rectosigmoid endometriosis

3D-TVS, non-enhanced (only BP)

Young et al 2017 (United States) – Overall high risk of bias

Rectosigmoid and/or rectovaginal septum

Very low-quality evidence from one study (n=57) found the sensitivity and specificity of 3D-TVS (non-enhanced, only BP) was 94% (70, 100) and 100% (91, 100) in diagnosing rectosigmoid and/or rectovaginal septum endometriosis.

Retrocervical and/or uterosacral ligament

Very low-quality evidence from one study (n=57) found the sensitivity and specificity of 3D-TVS (non-enhanced, only BP) was 86% (65, 97) and 94% (81, 99) in diagnosing rectosigmoid and/or uterosacral ligament endometriosis.

TVS, non-enhanced

Ros et al 2017 (Spain) – Overall high risk of bias

Rectosigmoid nodules

Very low-quality evidence from one study (n=40) found the sensitivity and specificity of TVS (non-enhanced) was 73% and 88% in diagnosing rectosigmoid nodule endometriosis.

TVS, non-enhanced (only BP)

Ros et al 2017 (Spain) – Overall high risk of bias

Rectosigmoid nodules

Very low-quality evidence from one study (n=40) found the sensitivity and specificity of TVS (non-enhanced, only BP) was 100% and 96% in diagnosing rectosigmoid nodule endometriosis.

TVS, enhanced (RWC)

Jiang et al 2017 (China) – Overall high risk of bias

Bowel and rectosigmoid

Very low-quality evidence from one study (n=198) found the sensitivity and specificity of TVS (non-enhanced, only BP) was 88.2% and 97.3% in diagnosing rectosigmoid nodule endometriosis.

Rectal scanning

Alborzi et al 2018 (Iran) – Overall high risk of bias

DIE

Very low-quality evidence from one study (n=317) found the sensitivity and specificity of TRS (non-enhanced, only BP) was 80.5% and 18.6 in diagnosing DIE.

USLs

Very low-quality evidence from one study (n=317) found the sensitivity and specificity of TRS (non-enhanced, only BP) was 82.8% and 89.8%in diagnosing USL endometriosis.

Rectal wall

Very low-quality evidence from one study (n=317) found the sensitivity and specificity of TRS (non-enhanced, only BP) was 86.5% and 97.7% in diagnosing rectal wall endometriosis.

Retrocervical

Very low-quality evidence from one study (n=317) found the sensitivity and specificity of TRS (non-enhanced, only BP) was 50% and 96.1% in diagnosing retrocervical endometriosis.

RV septum

Very low-quality evidence from one study (n=317) found the sensitivity and specificity of TRS (non-enhanced, only BP) was 84.1% and 93.8% in diagnosing RV septum endometriosis.

Ureter

Very low-quality evidence from one study (n=317) found the sensitivity and specificity of TRS (non-enhanced, only BP) was 100% and 100% in diagnosing ureter endometriosis.

Ovarian fossa

Very low-quality evidence from one study (n=317) found the sensitivity and specificity of TRS (non-enhanced, only BP) was 64.4% and 93.4% in diagnosing ovarian fossa endometriosis.

Bladder

Very low-quality evidence from one study (n=317) found the sensitivity and specificity of TRS (non-enhanced, only BP) was 100% and 99.7% in diagnosing bladder endometriosis.

Computed tomography

64-row CTC (CO_2 distension, iodinated contrast)

Baggio et al 2016 (Italy) – Overall high risk of bias

Bowel involvement

Very low-quality evidence from one study (n=37) found the sensitivity and specificity of 64-row CTC (CO_2 distension, iodinated contrast) was 68% and 67% in diagnosing bowel endometriosis.

64-row MSCT (water distension, iodinated contrast)

Iosca et al 2013 (Italy) – Overall high risk of bias and Stabile Ianora et al 2013 (Italy) – Overall high risk of bias

Bowel

Very low-quality evidence from two studies (n=97) found the sensitivity and specificity of 64-row MSCT (water distension, iodinated contrast) ranged from 87-100% and 97.6-100% respectively in diagnosing bowel endometriosis.

Iosca et al 2013 (Italy) – Overall high risk of bias

Ureteral

Very low-quality evidence from one study (n=64) found the sensitivity and specificity of 64-row MSCT (water distension, iodinated contrast) was 72.2% and 100% in diagnosing ureteral endometriosis.

16-row MDCT enteroclysis urography (iodinated contrast)

Biscaldi et al 2011 (Italy) – Overall high risk of bias

Bowel nodules

Very low-quality evidence from one study (n=103) found the sensitivity and specificity 16-row MDCT enteroclysis urography (iodinated contrast) was 95.5% and 97.2% in diagnosing endometriosis in bowel nodules.

Bowel nodules infiltrating at least the muscular layer

Very low-quality evidence from one study (n=103) found the sensitivity and specificity 16-row MDCT enteroclysis urography (iodinated contrast) was 93.3% and 96.6% in diagnosing endometriosis in bowel nodules infiltrating at least the muscular layer.

Ureteral compression

Very low-quality evidence from one study (n=103) found the sensitivity and specificity 16-row MDCT enteroclysis urography (iodinated contrast) was 97.1% and 98.8% in diagnosing endometriosis with ureteral compression

16-row MDCT (enema, iodinated contrast)

Ferrero et al 2011 (Italy) – Overall high risk of bias

Bowel

Very low-quality evidence from one study (n=96) found the sensitivity and specificity 16-row MDCT (enema, iodinated contrast) was 96.1% and 100% in diagnosing bowel endometriosis.

Rectosigmoid

Very low-quality evidence from one study (n=96) found the sensitivity and specificity 16-row MDCT (enema, iodinated contrast) was 95.8% and 100% in diagnosing bowel endometriosis

MRI

1.5-T MRI (gadolinium contrast)

Alborzi et al 2018 (Iran) – Overall high risk of bias

DIE

Very low-quality evidence from one study (n=317) found the sensitivity and specificity of 1.5-T MRI (gadolinium contrast) was 90.4% and 66.1% in diagnosing DIE.

USLs

Very low-quality evidence from one study (n=317) found the sensitivity and specificity of 1.5-T MRI (gadolinium contrast) was 63.58% and 93.98% in diagnosing USLs endometriosis.

Rectal wall

Very low-quality evidence from one study (n=317) found the sensitivity and specificity of 1.5-T MRI (gadolinium contrast) was 76.92% and 96.6% in diagnosing rectal wall endometriosis.

Retrocervical

Very low-quality evidence from one study (n=317) found the sensitivity and specificity of 1.5-T MRI (gadolinium contrast) was 65.79% and 96.42% in diagnosing retrocervical endometriosis.

RV septum

Very low-quality evidence from one study (n=317) found the sensitivity and specificity of 1.5-T MRI (gadolinium contrast) was 72.73% and 95.24% in diagnosing RV septum endometriosis.

Ureter

Very low-quality evidence from one study (n=317) found the sensitivity and specificity of 1.5-T MRI (gadolinium contrast) was 100% and 100% in diagnosing ureter endometriosis.

Ovarian fossa

Very low-quality evidence from one study (n=317) found the sensitivity and specificity of 1.5-T MRI (gadolinium contrast) was 66.1% and 98.06% in diagnosing ovarian fossa endometriosis.

Bladder

Very low-quality evidence from one study (n=317) found the sensitivity and specificity of 1.5-T MRI (gadolinium contrast) was 100% and 99.68% in diagnosing bladder endometriosis.

3-T MRI (no patient prep, no contrast)

Yap et al 2018 (Australia) – Overall high risk of bias

Any endometriosis

Very low-quality evidence from one study (n=37) found the sensitivity and specificity of 3-T MRI (no patient prep, no contrast) was 76.9% (69.7, 84.0) and 98.5% (97.3, 99.6) in diagnosing endometriosis.

Anterior compartment

Very low-quality evidence from one study (n=37) found the sensitivity and specificity of 3-T MRI (no patient prep, no contrast) was 33% (0, 86.7) and 100% (100, 100) in diagnosing anterior compartment endometriosis.

Posterior compartment

Very low-quality evidence from one study (n=37) found the sensitivity and specificity of 3-T MRI (no patient prep, no contrast) was 76.5% (66.4, 86.6) and 99.4% (98.1, 100) in diagnosing posterior compartment endometriosis.

Middle compartment

Very low-quality evidence from one study (n=37) found the sensitivity and specificity of 3-T MRI (no patient prep, no contrast) was 79.4% (69.4, 89.4) and 95.1% (91.2, 98.9) in diagnosing middle compartment endometriosis.

Rectosigmoid

Very low-quality evidence from one study (n=37) found the sensitivity and specificity of 3-T MRI (no patient prep, no contrast) was 94.4% (83.9, 100) and 94.7% (84.7, 100) in diagnosing rectosigmoid endometriosis.

Right ovary

Very low-quality evidence from one study (n=37) found the sensitivity and specificity of 3-T MRI (no patient prep, no contrast) was 100% (100, 100) and 85.0% (69.4, 100) in diagnosing right ovary endometriosis.

Left ovary

Very low-quality evidence from one study (n=37) found the sensitivity and specificity of 3-T MRI (no patient prep, no contrast) was 93.8% (81.9, 100) and 95.2% (86.1, 100) in diagnosing left ovary endometriosis.

Uterus

Very low-quality evidence from one study (n=37) found the sensitivity and specificity of 3-T MRI (no patient prep, no contrast) was 86.7% (69.5, 100) and 100% (100, 100) in diagnosing uterine endometriosis .

Biomarkers

Serum CA 125 >35 µg/mL

Baggio et al 2016 (Italy) – Overall high risk of bias =

Bowel

Very low-quality evidence from one study (n=92) found the sensitivity and specificity of biomarker testing (serum CA 125 >35 µg/mL) was 59% and 86% in diagnosing bowel endometriosis.

Surgical diagnosis

No new relevant diagnostic studies were identified

Q5b – Diagnosis of adenomyosis

What is the diagnostic performance of ultrasound and MRI in diagnosing adenomyosis?

Description of clinical evidence

This research question – focusing on diagnosis of adenomyosis – was not included in the NICE Guideline. The Research Protocol specifies that evidence prior to 2009 is not eligible. The literature search date was 21 October 2019.

Clinical evidence is summarised by intervention type, as classified in the Research Protocol:

- Ultrasound
- Pelvic magnetic resonance imaging (MRI)

Ultrasound

Five potentially relevant SRs were identified:

- Transvaginal ultrasound (TVUS), including 2D TVUS, 3D TVUS, elastography and colour Doppler (Andres et al 2018)
- Transvaginal sonography (TVS) or MRI (Bazot et al 2018)
- Diagnosis by any modality including ultrasound or MRI (Maheshwari et al 2012)
- TVUS or MRI (Champaneria et al 2010)
- TVS (Meredith et al 2009)

All five SRs included studies that were published before 2009 or did not meet the eligibility criteria specified in the Research Protocol.

Two relevant diagnostic studies were identified in the literature search and met the eligibility criteria:

- Ultrasound shear wave elastography (Acar et al 2016)
- 2D TVS with or without endomyometrial biopsy (Dakhly et al 2016)

An additional diagnostic study was identified that evaluated 3D ultrasound and colour Doppler for differentiating clinically suspected cases of leiomyoma and adenomyosis (Sharma et al 2015). This study was excluded because the study population was mixed (diagnosed as leiomyoma of uterus or adenomyosis based on clinical examination; none of the cases were clinically suspected to have both).

No test-and-treat trials were found, therefore no clinical or patient-reported outcomes such as quality of life were identified. The NICE Guideline Committee considered sensitivity and specificity as proxies for patient outcomes (indicating a benefit from a true negative or true positive finding).

Pelvic MRI

Two of the SRs listed above evaluated MRI in addition to ultrasound: Bazot et al (2018) and Champaneria et al (2010). All MRI studies included in these SRs were published before 2009.

No additional studies of MRI for the diagnosis of adenomyosis were identified in the literature search

Summary of included studies

Ultrasound

Table 34 Evidence Summary: Diagnosis of adenomyosis – ultrasound

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 35)
Full citation Acar S, Millar E, Mitkova M, Mitkov V. Value of ultrasound shear wave elastography in the diagnosis of adenomyosis. Ultrasound. 2016. 24:205-213. **Country** Russia **Aim** To assess the value of ultrasound shear wave elastography in the diagnosis of adenomyosis and to compare the obtained data with the results of morphological examination of operative material. **Study type** Retrospective **Study dates** Not reported **Source of funding** No financial support and no declared COIs	**Population** Retrospective analysis of 153 patients that underwent examination and treatment. Patients with suspected adenomyosis that underwent hysterectomy formed the main group. **Sample size** Main group n=53 underwent hysterectomy. 73.6% had adenomyosis by histology. Control group n=56 **Setting** Diagnostic Centre and Department of Surgical Gynecology at a hospital **Subgroup analysis** None **Inclusion criteria**[34] Suspected adenomyosis and hysterectomy with or without salpingo-oopherectomy. **Exclusion criteria** Not reported.	Index test: Ultrasound shear wave elastography (transvaginal and transabdominal) Reference standard: Histological examination of operative material from hysterectomy Prior tests: History. Not reported.	All patients underwent pelvic ultrasound according to standard protocol (transabdominal and transvaginal techniques). Ultrasound was performed before laparotomy in patients of the main group during the first phase of the menstrual cycle and on the day of admission to the hospital in cases of menopause. Aixplorer scanner with curved array transabdominal probe (operative frequency range 1–6 MHz) and curved array transvaginal probe (operative frequency range 3–12 MHz). Shear wave elastography was used in case of transvaginal examination with the endocavitary (transvaginal) transducer operating at a depth of ≤3 cm (technical limitations of this technique). Scanning was performed without additional compression movements of the hand and transducer. For histology, adenomyosis was defined microscopically by presence of ectopic endometrial glands and/or stroma in the myometrium, located 2.5 mm beyond the endometrial junction.	****No 2x2 data**** **Emean cut-off** Sensitivity: 89.7% (95%CI 75.8, 97.1) Specificity: 92.9% (95%CI 66.1, 99.8) AUC: 0.908 **Emax-cut off** Sensitivity: 89.7% (95%CI 75.8, 97.1) Specificity: 92.9% (95%CI 66.1, 99.8) AUC: 0.907	This technique may help to increase the accuracy of ultrasound in adenomyosis diagnosis, which could subsequently decrease the need for invasive diagnostic procedures, including hysterectomy. The addition of shear wave elastography to the transvaginal scan does not demand any significant lengthening of examination time; however, the main constraint at present is its field of operation, which is defined by the manufacturer and machine specifications, limited in this study to a depth of 3 cm. This would obviously have implications for large or axially orientated uteri. The technique is not suitable for women in whom transvaginal examination is contraindicated. Future studies with greater data should be considered to support the findings of this study and to confirm the proposed clinical benefit to patients and gynaecologists.	Patient selection: **High** (patients were not consecutive) Index Test: **High** (retrospective) Reference Standard: **Unclear** (if index test results were known) Flow and Timing: **Unclear** Potential applicability/ directness issues: **adenomyosis patients who undergo hysterectomy may have a different profile to those who do not; experience of person interpreting tests not reported** **Overall risk of bias assessment:** **High and small sample size**

[34] Inclusion criteria for the main group for the analysis

Study details	Participants	Diagnostic tests	Methods	Results	Authors conclusion	Risk of bias (Table 35)
Full citation Dakhly DMR, Abdel Moety GAF, Saber W, Gad Allah SH, Hashem AT, Abdel Salam LOE. Accuracy of hysteroscopic endomyometrial biopsy in diagnosis of adenomyosis. Journal of Minimally Invasive Gynecology. 2016. 23:364-371. **Country** Egypt **Aim** To investigate the diagnostic accuracy of endomyometrial biopsy obtained via office hysteroscopy for the diagnosis of adenomyosis. **Study type** Prospective **Study dates** January 2015 to August 2015 **Source of funding** Not reported	**Population** Premenopausal women with symptoms clinically suggestive of adenomyosis **Sample size** Women with suspected adenomyosis n=404 Number who underwent hysterectomy n=292 55.5% had adenomyosis on biopsy **Setting** University teaching hospital **Subgroup analysis** None **Inclusion criteria** Premenopausal women who presented with symptoms clinically suggestive of having adenomyosis (chronic pelvic pain, menorrhagia, menometrorrhagia, dysmenorrhoea, and/or dyspareunia) and subsequently underwent hysterectomy. **Exclusion criteria** Postmenopausal bleeding, pregnant women, and those who refused to be enrolled in the study.	Index test 1: 2D TVS Index test 2: Outpatient office hysteroscopy examination with endomyometrial biopsy Reference standard: Histopathologic findings in hysterectomy specimens. Adenomyosis was defined microscopically by the presence of ectopic endometrial glands and/or stroma in the myometrium, located 2.5mm beyond the endometrial junction Prior tests: Full history and thorough clinical examination	2D TVS performed by a single investigator using 7.5-MHz vaginal transducer of the Medison Sonoace X6. Performed in the postmenstrual period for patients with menorrhagia, and when the bleeding was minimal for metrorrhagia. Adenomyosis was diagnosed in presence of ≥2 of: heterogeneous myometrial echo-texture; a poorly defined endometrial–myometrial junction asymmetry of the anterior and posterior myometrium; subendometrial myometrial cysts; echogenic linear striations. Hysteroscopy was performed in the postmenstrual period by a single investigator blinded to TVS findings, using a ‘‘non-touch’’ or vaginoscopic approach with a 30° forward-oblique lens telescope and 5 mm outer diameter rigid continuous flow hysteroscope. Scissors were used to obtain a single square endomyometrial biopsy of diameter 10-20 mm from the posterior uterine wall. For hysterectomy specimens, 6-8 slides per area were obtained from the fundus, anterior, posterior, right and left lateral uterine walls, in addition to samples from macroscopically abnormal areas of myometrium. Assessment by a single pathologist blinded to ultrasound and hysteroscopic findings.	****No 2x2 data**** **TVS presence of ≥2 sonographic criteria** Sensitivity: 83.95% Specificity: 60% PPV: 72.34% NPV: 75% **Hysteroscopic appearance of uterine cavity** Sensitivity: 40.74% Specificity: 44.62% PPV: 47.83% NPV: 37.66% **Endomyometrial biopsy** Sensitivity: 54.32% Specificity: 78.46% PPV: 75.86% NPV: 57.95% **Combined TVS and endomyometrial biopsy** Sensitivity: 44.44% Specificity: 89.23% PPV: 83.72% NPV: 56.31%	The presence of myometrial cysts was the most specific sonographic criterion for diagnosing adenomyosis, followed by myometrial thickness asymmetry. The low sensitivity of endomyometrial biopsy is mostly related to the high false negative results commonly associated with cases with deep adenomyosis. Combining TVS with endomyometrial biopsy when both were positive improved specificity (89.23%). For clinical practice, we recommend that gynecologists start with TVS for patients who have symptoms suggestive of adenomyosis to obtain its benefit of high sensitivity; patients who are suspected to have the disease on TVS should be offered office hysteroscopy-guided endomyometrial biopsy. This sequential testing will offer a diagnosis with a high specificity. Thus, the patient with adenomyosis can be offered an accurate diagnosis in the setting of an outpatient procedure without the need for admission and with minimal complications, if any.	Patient selection: **Low** Index Test: **Low (TVS); Unclear (biopsy)** Reference Standard: **Unclear** Flow and Timing: **High** Potential applicability/ directness issues: **adenomyosis patients who undergo hysterectomy may have a different profile to those who do not; experience of person interpreting tests not reported** Overall risk of bias assessment: **High**

Abbreviations: AUC, area under the curve; CI, confidence interval; COI, conflict of interest; NPV, negative predictive value; PPV, positive predictive value; TCRE, transcervical resection of the endometrium; TVS, transvaginal sonography; 2D, two-dimensional; 3D, three-dimensional.

Table 35 QUADAS-2 Diagnostic accuracy checklist: Diagnosis of adenomyosis – ultrasound

Domain	Question	Acar et al 2016	Dakhly et al 2016
Patient selection			
Signalling questions	Was a consecutive or random sample of patients enrolled?	No	Yes
	Was a case-control design avoided?	No[35]	Yes
	Did the study avoid inappropriate exclusions?	No	Yes
Risk of Bias	Could the selection of patients have introduced bias?	**High**	**Low**
Concerns regarding applicability	Are there concerns that the included patients and setting do not match the review question?	High (not all patients with adenomyosis undergo hysterectomy)	High (not all patients with adenomyosis undergo hysterectomy)
Index Test			
Signalling questions	Were the index test results interpreted without knowledge of the results of the reference standard?	No (retrospective)	Yes
	If a threshold was used, was it pre-specified?	Yes	Yes, diagnostic criteria of adenomyosis defined
Risk of bias	Could the conduct or interpretation of the index test have introduced bias?	**High** (retrospective)	**Low** (TVS), **Unclear** (biopsy)
Concerns regarding applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear (level of experience of person interpreting test not reported)	High (level of experience of person interpreting test not reported; endomyometrial biopsy not common in Australia and unlikely to be acceptable)
Reference Standard			
Signalling questions	Is the reference standard likely to correctly classify the target condition?	Unclear (there are no agreed histological criteria for adenomyosis)	Unclear (there are no agreed histological criteria for adenomyosis)
	Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear	Yes
Risk of Bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	**Unclear**	**Unclear**
Concerns regarding applicability	Are there concerns that the target condition as defined by the reference standard does not match the question?	High (not all patients with adenomyosis undergo hysterectomy)	High (not all patients with adenomyosis undergo hysterectomy)
Flow and Timing			
Signalling questions	Was there an appropriate interval between index test and reference standard?	Yes	Yes
	Did all patients receive a reference standard?	Yes, all in main group	Yes
	Did all patients receive the same reference standard?	Yes, all in main group	Yes

[35] Control group was used for comparison of Young modulus numerical values.

Domain	Question	Acar et al 2016	Dakhly et al 2016
	Were all patients included in the analysis?	Unclear (2x2 tables not provided)	No (112 subjects were excluded: 64 subjects were given progesterone for dysfunctional uterine bleeding as proved by endometrial biopsy and the absence of other ultrasound abnormalities; 17 subjects declined hysterectomy; 31 subjects did not show up)
Risk of Bias	Could the patient flow have introduced bias?	**Unclear**	**High**

MRI

No relevant studies published from 2009 onwards were identified.

Evidence summaries

Ultrasound

Table 36 High level summary: Diagnosis of adenomyosis – ultrasound

Author Year	Country Setting	No. subjects Recruitment	Inclusion criteria	Method of ultrasound	Cases identified by reference standard	Overall risk of bias	Site(s) of endometriosis evaluated	Sensitivity% (95% CI)	Specificity% (95% CI)
Acar 2016	Russia hospital	53 Retrospective	Clinical suspicion of adenomyosis, that underwent hysterectomy	Ultrasound shear wave elastography (transvaginal and transabdominal)	73.6% adenomyosis	High	Adenomyosis	89.7[36] (75.8, 97.1)	92.9[36] (66.1, 99.8)
Dakhly 2016	Egypt University teaching hospital	292 Prospective	Clinical suspicion of adenomyosis, undergoing hysterectomy	2D TVS	55.5% adenomyosis	High	Adenomyosis	83.95	60

Abbreviations: CI, confidence interval; TVS, transvaginal sonography.
Note: For studies shown in grey text, 2x2 data (FP, FN, TP, TN) are not available.

MRI

No relevant studies published from 2009 onwards were identified.

[36] Using Emean cut-off

Clinical evidence profile

Ultrasound

Table 37 Evidence Profile Table: Diagnosis of adenomyosis – ultrasound

Index test	No. of studies *References*	No. of participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95% CI)	Specificity (95% CI)	Quality of the evidence (GRADE)
Ultrasound shear wave elastography	1 *Acar et al 2016*	53	Very serious risk of bias[1]	N/A	Serious indirectness[4]	No serious imprecision	89.7% (75.8, 97.1)	92.9% (66.1, 99.8)	Very low
2D TVS (presence of ≥2 sonographic criteria)	1 *Dakhly et al 2016*	292	Serious risk of bias[2]	N/A	Serious indirectness[4]	No serious imprecision[5]	83.95% (77, 89)[5]	60% (51, 68)[5]	Very low
Hysteroscopic appearance of uterine cavity	1 *Dakhly et al 2016*	292	Very serious risk of bias[3]	N/A	Serious indirectness[4]	No serious imprecision[5]	40.74% (33.5, 48.4)	44.62% (37.1, 54)	Low to Very low
Endomyometrial biopsy	1 *Dakhly et al 2016*	292	Very serious risk of bias[3]	N/A	Serious indirectness[4]	No serious imprecision[5]	54.32% (46.6, 61.8)	78.46% (70.6, 84.7)	Very low
Combined TVS and endomyometrial biopsy	1 *Dakhly et al 2016*	292	Very serious risk of bias[3]	N/A	Serious indirectness[4]	No serious imprecision[5]	44.44% (37, 52.1)	89.23% (82.7, 93.5)	Very low

Abbreviations: CI, confidence interval; N/A, not applicable; TVS, transvaginal sonography; 2D, two-dimensional.

1. Study did not use a consecutive or random sample; unclear if reference standard results were interpreted without knowledge of the results of the index tests; index test results were interpreted with knowledge of the reference standard results; unclear if all patients were included in the analysis.
2. Patients were excluded from the analysis; unclear if the interpretation of the reference standard could introduce bias.
3. Unclear if the conduct of the index test could have introduced bias; unclear if the interpretation of the reference standard could introduce bias; patients were excluded from the analysis.
4. Not all people with adenomyosis undergo hysterectomy (could be a severe subset); level of experience of person interpreting test not reported.
5. Variance not reported. 2 x 2 table and 95% CIs were calculated by the evidence reviewer.

MRI

No relevant studies published from 2009 onwards were identified.

Clinical evidence statements

Ultrasound

Ultrasound shear wave elastography

Acar et al 2016 (Russia) – Overall high risk of bias

Very low quality evidence from one RCT (n=53) found that ultrasound shear wave elastography has a sensitivity of 89.7% (95% CI: 75.8 to 97.1%) and specificity of 92.9% (95%CI: 66.1 to 99.8%) for the diagnosis of adenomyosis.

2D TVS (presence of ≥2 sonographic criteria)

Dakhly et al 2016 (Egypt) – Overall high risk of bias

Very low quality evidence from one RCT (n=292) found that 2D TVS (presence of ≥2 sonographic criteria) has a sensitivity of 83.95% (95%CI: 77 to 89%) and specificity of 60% (95%CI: 51 to 68%) for the diagnosis of adenomyosis.

MRI

No relevant studies published from 2009 onwards were identified.

Q6 – Systems that can guide treatment

Do staging systems to guide treatment in people with endometriosis improve patient outcomes?

Description of clinical evidence

The literature search date was 21 October 2019.

No new relevant studies were identified.

Q7a – Pharmacological management – Analgesics

In people with endometriosis or adenomyosis, are analgesics effective for managing endometriosis- or adenomyosis-associated pain?

Description of clinical evidence

The literature search date was 17 October 2019.

Endometriosis

No new relevant studies were identified.

Adenomyosis

No new relevant studies were identified.

Q7b – Pharmacological management – Neuromodulators

In people with endometriosis or adenomyosis, are neuromodulators effective for managing endometriosis- or adenomyosis- associated pain?

Description of clinical evidence

The literature search date was 16 October 2019.

Endometriosis

No new relevant studies were identified.

Adenomyosis

No new relevant studies were identified.

Q7c – Pharmacological management – Hormonal medical treatments

In people with endometriosis or adenomyosis, what is the effect of hormonal medical treatments on patient outcomes?

Description of clinical evidence

The literature search date was **15 October 2019**.

Clinical evidence is summarised by population:

- endometriosis
- endometriosis – after surgery
- adenomyosis

Endometriosis

Three new relevant SRs were identified:

- Combined hormonal contraceptives (Jensen et al 2018)
- Progesterone receptor modulators (mifepristone; Cochrane Review by Fu et al 2017)
- Elagolix (Pontis et al 2017)

Several broad SRs were also identified that investigated a range of interventions for endometriosis, including hormonal therapies (for example, Chen et al 2019; Chaichian et al 2017).

The identified SRs did not include any additional relevant RCTs that were missed from the literature search.

Six new relevant RCTs were identified:

Progestogen vs. placebo

- Dienogest vs. placebo (Lang et al 2018)

Progestogen vs. progestogen

- Etonogestrel (ENG)-releasing contraceptive implant (Implanon) vs. levonorgestrel-releasing intrauterine system (LNG-IUS) (Carvalho et al 2018)

Combined oestrogen/progestogen vs. progestogen vs. placebo

- Flexible Management of Intracyclic Bleeding ($Flexible_{MIB}$; ethinylestradiol + drospirenone) vs. dienogest (oral progestin) vs. placebo (Harada et al 2017)

Gonadotropin-releasing hormone (GnRH) receptor antagonist vs. placebo

- Elagolix vs. placebo (**two** RCTs reported in Taylor et al 2017)

GnRH receptor antagonist vs. GnRH agonist vs. placebo

- ASP1707 (Opigolix; GnRH receptor antagonist) vs. leuprorelin acetate (GnRH agonist) vs. placebo (D'Hooghe et al 2019)

Endometriosis – hormonal medical treatment after surgery

One new relevant RCT was identified:

Progestogen vs GnRH agonist

- Dienogest vs. leuprolide acetate (Abdou et al 2018)

Three additional trials were identified that examined the effect of hormonal medical treatments after surgery (Chen et al 2017; Tanmashasmut et al 2017; Huang 2018). These compare hormonal medical therapy with placebo or control and are captured under the evidence base for the research question on combination surgery plus hormonal treatment (Q9b).

Adenomyosis

One relevant SR was identified, but none of the included studies met the eligibility criteria:

- Medical treatment for adenomyosis (Pontis et al 2016)

Two new relevant RCTs were identified:

Progestogen vs. placebo

- Dienogest vs. placebo (Osuga et al 2017)

Progestogen vs. combined oestrogen/progestogen

- LNG-IUS vs. low dose combined oral contraceptive (COC) (Shaaban et al 2015)

Summary of included studies

Endometriosis

Six new relevant RCTs were identified. Four RCTs compared two different hormonal therapies, and three of those also included a placebo arm. Only one RCT had no placebo arm (Carvalho et al 2018). Three RCTs investigated progestogens (Lang et al 2018; Carvalho et al 2018; Harada et al 2017), one investigated combined oestrogen/progestogen (Harada et al 2017); three investigated GnRH receptor antagonists (Taylor et al 2017 [reports two RCTs]; D'Hooghe et al 2019), and one also investigated a GNRH agonist (D'Hooghe et al 2019).

Table 38 Evidence Summary: Hormonal medical treatments – Endometriosis

Study details	Participants	Intervention *(n)*	Methods	Results	Authors conclusion	Cochrane RoB tool
Progestogen vs. placebo						
Full citation Lang J, Yu Q, Zhang S, Li H, Gude K, von Ludwig C, Ren X, Dong L. Dienogest for treatment of endometriosis in Chinese women: A placebo-controlled, randomized, double-blind Phase 3 study. Journal of Women's Health. 2018. 27:148-155. **Country** China **Aim** To evaluate the efficacy and safety of dienogest in Chinese women. **F/U** 24 weeks **Source of funding** Study sponsored by Bayer	**Population** Chinese women with EAPP **Setting** 23 centres across China **Subgroup analysis** None **Inclusion criteria** 18–45 years with diagnosis of endometriosis confirmed by laparoscopy or laparotomy within 10 years before study entry; patients who reported VAS score ≥30 mm (on a 0–100 mm scale, where 100 = unbearable pain) for EAPP over past 4 weeks at screening visit and at randomisation. **Exclusion criteria** Pregnant or lactating; planning a pregnancy; had amenorrhoea (>3 months in the previous 6 months), undiagnosed genital bleeding, or evidence of therapy resistant endometriosis; recent use of hormonal agents[37]; required	**Group 1** Dienogest (oral progestin) *(n=130 randomised; n=126 full analysis set)*[38] **Group 2** Placebo *(n=132 randomised; n=129 full analysis set)*	Double-blinded treatment with once-daily oral dienogest 2mg or placebo for 24 weeks. Tablets of dienogest and placebo were identical in appearance. Supportive analgesic medication (ibuprofen 200 mg tablets) was permitted during the study.	**Mean change in EAPP from baseline to 24 weeks (VAS)** Dienogest: -38.7 mm (SD 25.07) Placebo: -15.7 mm (SD 24.09) LS MD: -24.54 mm (95% CI -29.93, -19.15) in favour of dienogest; p<0.0001 **Mean change in EAPP from baseline to 24 weeks (B&B)** Dienogest: -2.5 (SD 1.80) Placebo: -0.8 (SD 1.59) **Proportion of responders (25%, 50%, 75% reduction in VAS) between baseline and 24 weeks** Dienogest: 68.3%, 60.3%, 43.7% Placebo: 31.8%, 17.8%, 10.1% **Mean change in QoL from baseline to 24 weeks (SF-36)** *Physical component score* Dienogest: 4.99 (SD 6.13) Placebo: -0.04 (SD 4.43) *Mental component score* Dienogest: 1.86 (SD 8.23) Placebo: -0.87 (SD 7.32) **Change in intake of supportive analgesics in the previous 4**	Dienogest 2 mg once daily for 24 weeks was superior to placebo in reducing EAPP and was safe and well tolerated in Chinese women with endometriosis. The results are consistent with studies previously conducted in European women. A limitation of the double-blind phase of the study is the relatively short (24-week) treatment duration, as prolonged placebo treatment would be difficult to justify in women experiencing chronic pain.	Adequate sequence generation: **Insufficient information** Allocation concealment: **Low risk** Blinding: **Low risk** Incomplete outcome data addressed: **High risk** Free of selective reporting: **Low risk** Other bias: **None** *Dosage and administration consistent with Australian PI* **Overall: Serious risk of bias and short follow-up period**

[37] GnRH agonists within 6 months, long-acting agents such as depot progestins within 3 months, or short-acting agents such as oral contraceptives within 1 month.
[38] Full analysis set refers to subjects that received the allocated study drug. Used last observation carried forward to impute missing data.

Study details	Participants	Intervention *(n)*	Methods	Results	Authors conclusion	Cochrane RoB tool
	surgical treatment for endometriosis at the time of study inclusion.			**weeks from baseline to 24 weeks** Dienogest: -1.0 (SD 3.24) Placebo: +0.2 (SD 3.25) **Treatment satisfaction (much/very much satisfied)** Dienogest: 95 (75.4%) Placebo: 45 (34.9%) **Discontinuation due to AE** Dienogest: 2 (1.6%) Placebo: 2 (1.6%) **Study discontinuation** Dienogest: 18/130 (13.8%) Placebo: 19/132 (14.4%)		
Progestogen vs. progestogen						
Full citation Carvalho N, Margatho D, Cursino K, Benetti-Pinto CL, Bahamondes L. Control of endometriosis-associated pain with etonogestrel-releasing contraceptive implant and 52-mg levonorgestrel-releasing intrauterine system: randomized clinical trial. Fertility & Sterility. 2018. 110:1129-1136. **Country** Brazil **Aim** To assess the efficacy of an ENG-releasing contraceptive implant or the 52 mg LNG-IUS in the control of endometriosis-associated pelvic pain. **F/U** 6 months **Source of funding** Sao Paulo Research Council awards, Brazilian National Research Council grant.	**Population** Women with EAPP **Setting** Department of Obstetrics and Gynecology, University of Campinas Faculty of Medical Sciences, Campinas, **Subgroup analysis** None **Inclusion criteria** Surgically and histologically confirmed stage I–IV endometriosis[39] or diagnosis of deep endometriosis according to TVUS and MRI and complaints of noncyclic CPP and/or dysmenorrhoea for >6 months; clinically healthy, not pregnant, 18 and 45 years, able to keep a menstrual diary, willing to return for follow-up visits, willing to be randomised. **Exclusion criteria** Exclusion criteria established	**Intervention 1**: ENG-releasing contraceptive implant (Implanon, Merck) *(n=52 randomised; n=43 analysed)* **Intervention 2 (active comparator)**: LNG-IUS (Mirena, Bayer) *(n=51 randomised; n=39 analysed)*	The ENG implant (Implanon) or the LNG-IUS (52 mg 20 ug/d Mirena) were inserted within the first 5 days of the menstrual cycle. All subjects were followed up every 30±3 days after device insertion up to 6 months after insertion or until removal or expulsion of the intervention, whichever occurred first.	**Change in noncyclical pelvic pain VAS scores from baseline to 180 days** ENG Implant: MD 5.6 ± 1.7 (95% CI -6.4, -4.7); p<0.0001 LNG-IUS: MD 5.5 ± 1.6 (95% CI -6.2, -4.4); P<0.0001 No significant difference between groups: p=0.241 **Change in dysmenorrhoea VAS scores from baseline to 180 days** ENG Implant: MD 5.3 ± 1.3 (95% CI -6.6, -4.3); p<0.0001 LNG-IUS: MD 5.4 ± 1.3 (95% CI -6.3, -4.3); p<0.0001 No significant difference between groups: p=0.431 **Change in HRQoL (EHP-30 questionnaire) from baseline to 180 days** Statistically significant improvement in all domains in both groups[41]but no difference between groups	The study found no significant differences between the ENG subdermal contraceptive implant and the 52 mg 20 ug/d LNG-IUS in improving pelvic pain and dysmenorrhoea and increasing health-related QoL in women with EAPP and deep endometriosis. Both treatments are long-term feasible options for women with EAPP, with few side effects. Nevertheless, further studies are required, particularly with respect to the ENG implant, to enable long-term effects of this treatment to be assessed in a larger sample.	Adequate sequence generation: **Low risk** Allocation concealment: **Low risk** Blinding: **High risk** Incomplete outcome data addressed: **Some concerns** Free of selective reporting: **Low risk** Other bias: **No placebo/control** **Overall: Serious risk of bias, small study with short follow-up**

[39] Based on the Revised American Fertility Society Classification of Endometriosis

[41] With the exception of feelings about possibility of not conceiving in LNG-IUS group (p=0.0837).

Study details	Participants	Intervention *(n)*	Methods	Results	Authors conclusion	Cochrane RoB tool
One author (LB) received an honorarium to be a member of an advisory board for Bayer and Merck.	by the WHO[40]; women who had undergone surgical or hormonal treatments for endometriosis within 2 months of enrollment in the study.			**Discontinuation due to AE** No AEs occurred during insertion **Study discontinuation and lost to follow-up** ENG implant: 9/52 (17.3%), includes 5 lost to F/U, 4 removed LNG-IUS: 12/5 (23.5%), includes 6 lost to F/U, 2 removed, 4 expulsions		
Combined oestrogen/progestogen vs. progestogen vs. placebo						
Full citation Harada T, Kosaka S, Elliesen J, Yasuda M, Ito M, Momoeda M. Ethinylestradiol 20 ug/drospirenone 3 mg in a flexible extended regimen for the management of endometriosis-associated pelvic pain: a randomized controlled trial. Fertility & Sterility. 2017. 108:798-805. **Country** Japan **Aim** To investigate the efficacy and safety of ethinylestradiol 20 ug/drospirenone 3 mg in a flexible extended regimen ($Flexible_{MIB}$) compared with placebo to treat EAPP. **F/U** Part 1: 24-week blinded trial Part 2: 28-week OL extension **Source of funding** Bayer funded the trial and participated in trial design and managed all operational aspects (monitoring data collection,	**Population** Women with EAPP **Setting** 32 centres **Subgroup analysis** None **Inclusion criteria** Aged ≥20 years; diagnosis of endometriosis[42]; pelvic pain VAS score ≥ 40 mm; regular menstrual cycles. **Exclusion criteria** Surgical treatment for endometriosis within 2 months; APS; regular use of analgesics for reasons other than endometrial pain (occasional use permitted but not prophylaxis); endometriomas with solid components or >10 cm and aged ≥40 years; diseases or conditions likely to worsen under hormonal treatment; receipt of hormone preparations[43] or St. John's Wort within 2 months; breastfeeding; pregnant;	*Subjects were randomised in a 2.5:2.5:1 ratio* **Intervention 1**: Flexible management of intracyclic bleeding ($Flexible_{MIB}$) *(Part 1 RCT n=130 randomised; n=104 completed; Part 2 OL n=85 completed)* **Intervention 2**: Placebo *(Part 1 RCT n=129 randomised; n=111 completed; Part 2 OL n=87 completed)* **Intervention 3** Dienogest (unblinded reference arm to compare vaginal bleeding pattern) *(Part 1 RCT n=53 randomised; n=45 completed; Part 2 OL n=45 completed)*	**$Flexible_{MIB}$** Ethinylestradiol 20 ug/ drospirenone 3 mg. One tablet per day, starting between the first and fifth day of menstruation. Tablets were administered continuously for 120 days, followed by a 4-day tablet-free interval. In the event of ≥3 consecutive days of spotting and/or bleeding on days 25–120 of the cycle, patients began and completed the 4-day tablet-free interval, then started the next cycle of treatment. **Placebo** One tablet daily following the same instructions as the $Flexible_{MIB}$ group for 24 weeks, then switched to $Flexible_{MIB}$ for the OL extension phase. **Dienogest** One tablet twice daily at a total daily dose of 2 mg	**Mean change in VAS severest EAPP to 24 wks** $Flexible_{MIB}$: -36.6 (SD 23.9; 95% CI-41.1, -32.2) Placebo: -10.7 (SD 18.0; 95% CI -14.0, -7.4) Dienogest: -50.0 (SD 25.0; 95% CI-57.2, -42.9) LS MD $Flexible_{MIB}$ vs. placebo: -26.3 (95% CI -31.6, -20.9); p<.0001 Dienogest more efficacious. **Days requiring rescue medication Week 8-12** No difference $Flexible_{MIB}$ vs. placebo **Patient satisfaction (highly/very highly satisfied)** $Flexible_{MIB}$: 43.1% Placebo: 10.3% **Study discontinuation 24 wks** $Flexible_{MIB}$: 26/130 (20.0%) Placebo: 17/129 (13.2%) Dienogest: 8/53 (15.1%) **Discontinuation due to AE** $Flexible_{MIB}$: 12/130 (9.2%) Placebo: 2/128 (1.6%) Dienogest: 0/53 (0%)	$Flexible_{MIB}$ improved EAPP and was well tolerated, suggesting it may be a new alternative for managing endometriosis. Over the 180-day study period, the number of bleeding/ spotting days in the $Flexible_{MIB}$ group was similar to the placebo group but markedly smaller than the dienogest group. Dienogest showed good efficacy and was well tolerated. An effective double-blind design with dienogest was considered inappropriate because of differences in dosing, the flexible intake regimen of the study drug, and expected bleeding patterns.	Adequate sequence generation: **Low risk** Allocation concealment: **Insufficient information** Blinding: **High risk** Incomplete outcome data addressed: **High risk** Free of selective reporting: **Low risk** Other bias: **None** *Menstrual pattern may have effectively 'unblinded' the patient.* **Overall: Very serious risk of bias**

[40] World Health Organization. Medical eligibility criteria for contraceptive use, Reproductive Health and Research. 5th ed. Geneva: World Health Organization; 2015.

[42] Clinical diagnosis of endometriosis and pelvic tenderness, induration in the cul de sac, or uterine immobility, as well as diagnosis by laparotomy/laparoscopy or by identification of endometriomas.

[43] Includes hormonal preparations containing progestin, estrogen, GnRH analogues, testosterone derivatives, estrogen antagonists, aromatase inhibitors, medications or their derivatives that were presumed to affect the secretion of sex hormones.

Study details	Participants	Intervention *(n)*	Methods	Results	Authors conclusion	Cochrane RoB tool
statistical analyses and writing of the report)	undiagnosed abnormal vaginal bleeding; smokers[44].					
GnRH receptor antagonist vs. placebo						
Full citation Taylor HS, Giudice LC, Lessey BA, Abrao MS, Kotarski J, Archer DF, Diamond MP, Surrey E, Johnson NP, Watts NB, Gallagher JC, Simon JA, Carr BR, Dmowski WP, Leyland N, Rowan JP, Duan WR, Ng J, Schwefel B, Thomas JW, Jain RI, Chwalisz K. Treatment of endometriosis-associated pain with elagolix, an oral GnRH antagonist. New England Journal of Medicine. 2017. 377:28-40. **Country** Unites States and Canada **Aim** To evaluate the effects of two doses of elagolix as compared with placebo in women with surgically diagnosed endometriosis and moderate or severe EAPP **F/U** 6 months **Source of funding** The sponsor, AbbVie, designed the trials and analysed the data. Elaris EM-I ClinicalTrials.gov number NCT01620528	**Population** Women with moderate or severe EAPP **Setting** Multicentre and multinational study (151 sites) **Subgroup analysis** None **Inclusion criteria** Premenopausal women aged 18 to 49 years; surgical diagnosis of endometriosis in the previous 10 years; menstrual cycle 24-38 days; moderate or severe dysmenorrhoea or NMPP[45]. **Exclusion criteria** History of osteoporosis or other metabolic bone disease; clinically significant gynecologic conditions or chronic pain conditions unrelated to endometriosis; pregnant or breastfeeding; history of non-response to GnRH agonists, antagonists, aromatase inhibitors, depot medroxyprogesterone acetate; IUD.	**Elaris EM-I (N=872)** *Subjects were randomised in a 2:2:3 ratio* **Group 1** Elagolix 150 mg *(n=249 randomised; n=196 completed)* **Group 2** Elagolix 200 mg *(n=248 randomised; n=183 completed)* **Group 3** Placebo *(n=374 randomised; n=274 completed)*	Treatment consisted of two doses of elagolix — 150 mg once daily (lower-dose group) and 200 mg twice daily (higher-dose group). No details are provided about the appearance or dosing of the placebo. The trial was divided into three intervals: a washout of hormonal therapies (if applicable); a screening period of up to 100 days, including two menstrual cycles, during which women switched from the use of usual analgesic agents to receive allowed rescue medication of an NSAID (500 mg of naproxen), an opioid according to country or both; a 6-month treatment period.	**LS mean change in EAPP (NRS) from baseline to 3 mo** Elagolix 150: -1.74 (SE 0.12) Difference from placebo: - 0.65 (SE 0.16); p<0.001 Elagolix 200: -2.39 (SD 0.12) Difference from placebo: - 1.30 (SE 0.16); p<0.001 Placebo: -1.09 (SE 0.10) **Clinically meaningful reduction in dysmenorrhoea and decreased or stable use of rescue analgesics at 3 mo** Elagolix 150: 46.4%; p<0.001 Elagolix 200: 75.8%; p<0.001 Placebo: 19.6% **Clinically meaningful reduction in NMPP and decreased or stable use of rescue analgesics at 3 mo** Elagolix 150: 50.4%; p<0.001 Elagolix 200: 54.5%; p<0.001 Placebo: 36.5% **Study discontinuations 6 mo** Elagolix 150: 21% Elagolix 200: 26% Placebo: 27% **Discontinuation due to AE** Elagolix 150: 16/249 (6.4%) Elagolix 200: 23/248 (9.3%) Placebo: 22/374 (5.9%)	The use of elagolix resulted in reductions in two of the hallmark pain symptoms of endometriosis, dysmenorrhoea and NMPP, after both 3 months and 6 months. Consistent with the mechanism of action, elagolix treatment resulted in hypoestrogenic effects, including hot flushes and changes in bone mineral density and lipids. Women who received the higher dose of elagolix had significantly better results with respect to the use of rescue analgesic agents at 3 and 6 months, dyspareunia at 3 months, and rescue opioid use at 3 months than did those receiving placebo. The observed improvements in QoL were consistent with the primary and key secondary endpoints.	Adequate sequence generation: **Low risk** Allocation concealment: **Low risk** Blinding: **Insufficient information** Incomplete outcome data addressed: **High risk** Free of selective reporting: **Low risk** Other bias: **None** *Elagolix is not yet TGA-approved.* **Overall: Serious risk of bias and short follow-up**
Full citation Taylor et al 2017 *As for Elaris EM-I* **Country** 5 continents	**Population** Women with moderate or severe EAPP	**Elaris EM-II (N=817)** **Group 1** Elagolix 150 mg *(n=226 randomised; n=178 completed)*	*As for Elaris EM-I*	**LS mean change in EAPP (NRS) from baseline to 3 mo** Elagolix 150: -1.90 (SE 0.12) Difference from placebo: - 0.57 (SE 0.16); p<0.001 Elagolix 200: -2.55 (SD 0.12)	*As for Elaris EM-I*	*As for Elaris EM-I* *Elagolix is not yet TGA-approved.*

[44] Smokers aged > 35 years or ≥ 15 cigarettes/day.

[45] Assessed using the Composite Pelvic Signs and Symptoms Score, average daily diary score, Monthly Assessment of Endometriosis Pain, and e-Diary entries in the last 35 days of the screening period.

Study details	Participants	Intervention *(n)*	Methods	Results	Authors conclusion	Cochrane RoB tool
Aim To evaluate the effects of two doses of elagolix as compared with placebo in women with surgically diagnosed endometriosis and moderate or severe EAPP. **F/U** 6 months **Source of funding** The sponsor, AbbVie, designed the trials and analysed the data. Elaris EM-II ClinicalTrials.gov number NCT01931670	**Setting** Multicentre and multinational study (187 sites) **Subgroup analysis** None **Inclusion criteria** *As for Elaris EM-I* **Exclusion criteria** *As for Elaris EM-I*	**Group 2** Elagolix 200 mg *(n=229 randomised; n=184 completed)* **Group 3** Placebo *(n=360 randomised; n=270 completed)*		Difference from placebo: - 1.22 (SE 0.16); p<0.001 Placebo: -1.33 (SE 0.10) **Clinically meaningful reduction in dysmenorrhoea and decreased or stable use of rescue analgesics at 3 mo** Elagolix 150: 43.4%; p<0.001 Elagolix 200: 72.4%; p<0.001 Placebo: 22.7% **Clinically meaningful reduction in NMPP and decreased or stable use of rescue analgesics at 3 mo** Elagolix 150: 49.8%; p=0.003 Elagolix 200: 57.8%; p<0.001 Placebo: 36.5% **Study discontinuations 6 mo** Elagolix 150: 21% Elagolix 200: 20% Placebo: 25% **Discontinuation due to AE** Elagolix 150: 10/226 (4.4%) Elagolix 200: 23/229 (10.2%) Placebo: 22/360 (6.1%)		**Overall: Serious risk of bias and short follow-up**
GnRH receptor antagonist vs. GnRH agonist vs. placebo						
Full citation D'Hooghe T, Fukaya T, Osuga Y, Besuyen R, Lopez B, Holtkamp GM, Miyazaki K, Skillern L. Efficacy and safety of ASP1707 for endometriosis-associated pelvic pain: the phase II randomized controlled TERRA study. Human Reproduction. 2019. 34:813-823. **Country** Europe and Japan	**Population** Women with EAPP **Setting** Multicentre and multinational study **Subgroup analysis** None **Inclusion criteria** Women aged 18–45 years; moderate-to-severe endometriosis-associated dysmenorrhoea and NMPP;[46] surgically confirmed diagnosis	**Group 1** ASP1707 (Opigolix) 3 mg *(Part 1 n=87 randomised; n=86 received/analysed* **Group 2** Opigolix 5 mg *(Part 1 n=92 randomised, n=91 analysed)* **Group 3** Opigolix 10 mg *(Part 1 n=90 randomised; n=90 analysed)*	**Part 1** All patients randomised to Opigolix (orally active GnRH antagonist) or placebo took 3 tablets once daily in the morning (Opigolix 15 mg group: 3 × 5 mg tablets; Opigolix 10 mg group: 2 × 5 mg tablets and 1 placebo tablet; Opigolix 5 mg group: 1 × 5 mg tablet and 2 placebo tablets; Opigolix 3 mg group: 3 × 1 mg tablets; placebo group: 3 placebo	**Part 1 Mean difference in NRS Pain Score[47] from baseline to 12 weeks (vs. placebo)** Opigolix 3 mg: -0.07 (SE 0.25; 95% CI -0.68, 0.54) Opigolix 5 mg: -0.37 (SE 0.24; 95% CI -0.96, 0.22) Opigolix 10 mg: -0.73 (SE 0.24; 95% CI-1.32, -0.13); p=0.011 Opigolix 15 mg: -0.57 (SE 0.24; 95% CI -1.17, 0.02) **Part 1 Mean difference in NMPP (Modified B&B) from baseline to 12 weeks**	ASP1707 is a potential alternative treatment to leuprorelin for EAPP with lower impact on bone health. All doses of ASP1707 reduced serum E2 levels to within the target range and to a lesser extent than leuprorelin. A placebo response was observed in all pain endpoints. Subjects receiving placebo	Adequate sequence generation: **Low risk** Allocation concealment: **Low risk** Blinding: **Low risk** (all groups double blind except for Group 5) Incomplete outcome data addressed: **Insufficient information** Free of selective reporting: **Low risk**

[46] Subject was suffering from endometriosis-associated dysmenorrhoea and NMPP (NRS>0 in both domains), with at least one of the following: (a) moderate to severe dysmenorrhoea (mean NRS ≥4 over all menstrual days); (b) moderate NMPP (NRS ≥4 on at least 7 non-menstrual days; (c) confirmed menstrual cycle length (24-35 days inclusive).

[47] NRS (0, no pain; 10, worst imaginable pain) for overall pelvic pain

Study details	Participants	Intervention *(n)*	Methods	Results	Authors conclusion	Cochrane RoB tool
Aim Part 1: To assess the efficacy and dose–response relationship of ASP1707 in reducing endometriosis-associated pelvic pain at the end of treatment Part 2: To assess the safety, tolerability, PK, and the dose–response relationship of ASP1707 in reducing serum E2 levels. **F/U** Part 1: 12 weeks Part 2: 12 weeks **Source of funding** Astellas Pharma Inc. TD'H is Vice President and Head of Global Medical Affairs Fertility at Merck, Germany	of endometriosis within 5 years; confirmed regular menstrual cycle of 24–35 days. **Exclusion criteria** Treatments that alter gynecological endocrinology; surgery for endometriosis within 4 weeks of study initiation; presence of gynecological or pelvic abnormalities; concurrent disease with chronic abdominal pain of non-endometriosis origin; concurrent or previous osteoporosis, bone loss, other metabolic bone diseases; other clinically significant condition.	**Group 4** Opigolix 15 mg *(Part 1 n=90 randomised; n=88 analysed)* **Group 5** Leuprorelin acetate *(Part 1 n=92 randomised; n=89 analysed)* **Group 6** Placebo *(Part 1 n=89 randomised; n=88 analysed)*	tablets). All tablets were identical in size, appearance and dimensions. Leuprorelin acetate (PROSTAP SR depot) was administered via subcutaneous injection (3.75 mg/month) **Part 2** Subjects randomised to placebo for Part 1 were also randomised to one of four Opigolix doses for Part 2.	Placebo: -0.72 (95% CI -0.88, - 0.56) Opigolix 3 mg: -0.81 (95% CI - 0.98, - 0.65), p=0.831 Opigolix 5 mg: -0.98 (95% CI - 1.14, -0.83), p=0.055 Opigolix 10 mg: -1.01, (95% CI - 1.17, -0.85), p=0.033 Opigolix 15 mg: -1.09 (95% CI - 1.25, -0.94), p=0.003 Treatment effect[48]: p<0.001 Leuprorelin: -1.26 (95% CI - 1.42, -1.10) **Part 1 Mean difference in dysmenorrhoea (Modified B&B) from baseline to 12 weeks** Placebo: -0.66 (95% CI -0.85, - 0.47) Opigolix 3 mg: -1.12 (95% CI - 1.32, - 0.92), p=0.004 Opigolix 5 mg: -1.20 (95% CI - 1.38, -1.01), p<0.001 Opigolix 10 mg: -1.53, (95% CI - 1.73, -1.34), p<0.001 Opigolix 15 mg: -1.70 (95% CI - 1.89, -1.51), p<0.001 Treatment effect: p<0.001 Leuprorelin: -2.08 (95% CI - 2.26, -1.91) **Study discontinuation** Opigolix 3 mg: 16/87 (18.4%) Opigolix 5 mg: 8/92 (8.7%) Opigolix 10 mg: 14/90 (15.6%) Opigolix 15 mg: 15/90 (16.7%) Leuprorelin: 16/92 (17.4%) Placebo: 14/89 (15.7%) **Discontinuation due to AE** Opigolix 3 mg: 3/86 (3.5%) Opigolix 5 mg: 0/91 (0%) Opigolix 10 mg: 1/90 (1.1%) Opigolix 15 mg: 5/88 (5.7%) Leuprorelin: 1/89 (1.1%) Placebo: 0/88 (0%)	experienced a 39% decrease from baseline in overall pelvic pain, a 26% decrease in dysmenorrhoea and a 40% decrease in NMPP at 12 weeks. This study does have limitations to be considered. While Part 1 of the study included a placebo group, the study was not powered to make pairwise comparisons of each ASP1707 group versus placebo.	Other bias: **Clinical practice may differ between countries** *Opigolix is not TGA-approved* *The PROSTAP SR depot dose is different to other TGA-approved leuprorelin formulations* **Overall: Moderate risk of bias and small sample size for each dose**

[48] Overall treatment effect from linear trend across placebo and ASP1707 groups.

Abbreviations: AE, adverse event; APS, anti-phospholipid antibody syndrome; B&B, Biberoglu and Behrman; CI, confidence interval; CPP, chronic pelvic pain; EAPP, endometriosis-associated pelvic pain; EHP, Endometriosis Health Profile-5; ENG, etonogestrel; F/U, follow up; GnRH, gonadotropin-releasing hormone; LNG-IUS, levonorgestrel-releasing intrauterine system; LS, least squares; MD, mean difference; mo, month; MRI, magnetic resonance imaging; NMPP, nonmenstrual pelvic pain; NRS, numerical rating scale; OL, open label; PI, Product Information; QoL, quality of life; RCT, randomised controlled trial; SD, standard deviation; SE, standard error; SF-36, 36-item Short Form health survey – version 2, TVUS, transvaginal ultrasonography; VAS, visual analogue scale; WHO, World Health Organization.

Endometriosis – hormonal medical treatment after surgery

One new relevant RCT was identified that compared a progestogen (dienogest) with a GnRH agonist (leuprolide acetate) in people with recurrent pelvic pain following laparoscopic surgery for endometriosis-associated pelvic pain (Abdou et al 2018).

Table 39 Evidence Summary: Hormonal medical treatments – Endometriosis – after surgery

Study details	Participants	Intervention *(n)*	Methods	Results	Authors conclusion	Cochrane RoB tool
Progestogen vs. GnRH agonist						
Full citation Abdou AM, Ammar IMM, Alnemr AAA, Abdelrhman AA. Dienogest versus leuprolide acetate for recurrent pelvic pain following laparoscopic treatment of endometriosis. Journal of Obstetrics & Gynaecology of India. 2018. 68:306-313. **Country** Egypt **Aim** To compare the efficacy of dienogest with depot leuprolide acetate in patients with recurrent pelvic pain following laparoscopic surgery for endometriosis. **F/U** 12 weeks **Source of funding** Not reported. The authors declared no COI.	**Population** Patients with recurrent pelvic pain following laparoscopic surgery for EAPP. **Setting** Department of Obstetrics and Gynecology, Faculty of medicine, Zagazig University hospitals **Subgroup analysis** None **Inclusion criteria** Women aged 20–45 years with recurrent pelvic pain within 1 year following laparoscopic surgery for histopathologically proven endometriosis;[49] endometriosis confirmed by diagnostic laparoscopy within 3 months or by therapeutic laparoscopy within 12 months of enrollment with subsequent recurrence of pain. **Exclusion criteria** Pregnancy; breast feeding; amenorrhea within 3 months of enrollment; previous use of hormonal agents (e.g. GnRH agonists, progestins, danazol or	**Group 1** Dienogest *(n=130 randomised, n=121 full analysis set)* **Group 2** Leuprolide acetate *(n=131 randomised, n=121 full analysis set)*	**Group 1** Patients received dienogest at a dose of 2 mg given orally once daily at the same time for 12 weeks with the first tablet taken on the first day after onset of menstrual bleeding. **Group 2** Patients received leuprolide acetate at a standard dose of 3.75 mg as a depot intramuscular injection every 4 weeks for 12 weeks with the first injection given during the first 3 days of menstrual bleeding.	**Mean pelvic pain (VAS 0-100)**[50] Dienogest *(n=101)* Baseline: 59.27 ± SD 11.02 12 weeks: 30.61 ± 10.65 Paired t: 32.348; p<0.001 Leuprolide acetate *(n=96)* Baseline: 58.73 ± 11.01 12 weeks: 32.53 ± 8.74 Paired t: 83.246; p<0.001 Difference between groups Baseline: T=0.343, p=0.732 12 weeks: T=-1.377; p= 0.170 **Mean back pain (VAS 0-100)** Dienogest *(n=72)* Baseline: 45.91 ± 3.33 12 weeks: 26.92 ± 4.40 Paired t: 37.476; p<0.001 Leuprolide acetate *(n=68)* Baseline: 46.68 ± 3.29 12 weeks: 27.22 ± 1.79 Paired t: 51.714; p<0.001 Difference between groups Baseline: T=-1.358, p=0.177 12 weeks: T=-0.529; p=0.597 **Mean dyspareunia (VAS 1-100)** Dienogest *(n=55)* Baseline: 36.53 ± 3.87	Daily dienogest is as effective as depot leuprolide acetate for relieving EAPP, low back pain and dyspareunia. In addition, dienogest has acceptable safety, tolerability and lower incidence of hot flushes. Thus, it may offer an effective and well-tolerated treatment in endometriosis.	Adequate sequence generation: **Low risk** Allocation concealment: **Low risk** Blinding: **High risk** Incomplete outcome data addressed: **High risk (differs per outcomes, explanations not given)** Free of selective reporting: **Low risk** Other bias: **None** **Overall: Serious risk of bias and short follow-up**

[49] Revised American Fertility Society (r-AFS, 1985) stages I–IV based on the total surface size of the lesions, presence of adhesions, and ovarian lesions.
[50] Percentages in groups were compared by Chi-square test and differences between parametric quantitative independent groups by t test in pairs by paired t.

Study details	Participants	Intervention *(n)*	Methods	Results	Authors conclusion	Cochrane RoB tool
	oral contraceptives) following laparoscopy; undiagnosed genital bleeding; history of severe adverse drug reactions or hypersensitivity to steroid hormones or GnRH agonists; history of thrombosis/embolism or depression and patients at risk of decreased BMD.			12 weeks: 16.53 ± 3.10 Paired t: 48.076; p<0.001 Leuprolide acetate *(n=62)* Baseline: 34.98 ± 4.96 12 weeks: 17.11 ± 2.53 Paired t: 25.656; p<0.001 Difference between groups Baseline: T=1.859, p=0.066 12 weeks: T=-1.125; p= 0.263 **Study discontinuation (all lost to follow up)** Dienogest: 9/130 (6.9) Leuprolide acetate: 10/131 (7.6%) **Discontinuation due to AE** No patients discontinued due to abnormal uterine bleeding		

Abbreviations: AE, adverse events; BMD, bone mineral density; COI, conflict of interest; EAPP, endometriosis-associated pelvic pain; F/U, follow up; GnRH, Gonadotrophin-releasing hormone; RoB, risk of bias; VAS, visual analogue scale.

Adenomyosis

Two new relevant RCTs were identified: dienogest versus placebo (Osuga et al 2017); and LNG-IUS versus low dose COC (Shaaban et al 2015).

Table 40 Evidence Summary: Hormonal medical treatments – Adenomyosis

Study details	Participants	Intervention *(n)*	Methods	Results	Authors conclusion	Cochrane RoB tool
Progestogen vs. placebo						
Full citation Osuga Y, Fujimoto-Okabe H, Hagino A. Evaluation of the efficacy and safety of dienogest in the treatment of painful symptoms in patients with adenomyosis: a randomized, double-blind, multicenter, placebo-controlled study. Fertility & Sterility. 2017. 108:673-678. **Country** Japan **Aim** To evaluate the efficacy and safety of dienogest (DNG), a progestational 19-norsteroid, in patients with symptomatic adenomyosis. **F/U** 16 weeks **Source of funding** Sponsored by Mochida Pharmaceuticals	**Population** Women with symptomatic adenomyosis **Setting** Multicentre study (20 sites) **Subgroup analysis** None **Inclusion criteria** Aged ≥20 years; regular menstrual cycles ≤38 days; adenomyosis diagnosed by imaging (both MRI and TVS); pain symptoms (lower abdominal pain and/or lumbago) scoring three points or more on the verbal pain rating scale during the menstrual cycle. **Exclusion criteria** Endometriosis or uterine leiomyoma diagnosed by imaging (both MRI and TVS); severe anaemia; marked uterine enlargement[51].	**Group 1** Dienogest *(n=35 randomised; n=34 received/ analysed)* **Group 2** Placebo *(n=33 randomised; n=33 analysed)*	Patients received a 1 mg dienogest tablet or an identical placebo tablet twice daily for 16 weeks, starting between the second and fifth day of the menstrual cycle. Patients were allowed to take analgesics for the duration of the study. Gynaecologists with ample experience of image diagnosis were selected as study investigators. No specific criteria for adenomyosis based on TVS and MRI were selected. Adenomyosis was diagnosed by investigators and no central determination was made by image specialists.	**Mean change in EAPP from baseline to 16 weeks (VAS)[52]** Dienogest: -58.4 mm (SD 23.6) Placebo: -20.6 mm (SD 23.6); p<0.001 **Mean change in pain score from baseline to 16 weeks[53]** Dienogest: -3.8 (SD 1.9) Placebo: -1.4 (SD 1.8); p<0.001 **Mean change in pain severity score from baseline to 16 weeks** Dienogest: -1.9 (SD 1.0) Placebo: -0.6 (SD 0.8); p<0.001 **Mean change in QoL (SF-36) from baseline to 16 weeks** Significant difference between groups in role physical and bodily pain but not other domains **Study discontinuation** Dienogest: 3/35 (8.6%) Placebo: 3/33 (9.1%) **Discontinuation due to AE** Dienogest: 1/34 (2.9%) due to hot flushes and menopausal symptoms Placebo: 1/33 (3.0%) due to irregular uterine bleeding	These results suggest that dienogest is effective and well tolerated in the treatment for painful symptoms associated with adenomyosis not complicated by severe uterine enlargement or severe anemia.	Adequate sequence generation: **Low risk** Allocation concealment: **Low risk** Blinding: **Low risk** Incomplete outcome data addressed: **Low risk** Free of selective reporting: **Moderate risk (mean difference between groups not reported)** Other bias: **None** **Overall: Moderate risk of bias, small sample size and short follow-up**
Progestogen vs. combined oestrogen/progestogen						
Full citation Shaaban OM, Ali MK, Sabra AM, Abd El Aal DE. Levonorgestrel-releasing intrauterine system versus a low-dose combined oral contraceptive for treatment of	**Population** Women with adenomyosis-associated pelvic pain **Setting** Outpatient Gynecology Clinic	**Group 1** LNG-IUS (Mirena) *(n=31 randomised; n=29 analysed)*	The LNG-IUS group received Mirena (Bayer Schering Healthcare), inserted according to the manufacturer's instructions. TVS ascertained	**Mean pelvic pain (VAS)** LNG-IUS: Baseline 6.23 (SD 0.67); at 6 months 1.68 (SD 1.25); p<0.001 COC: Baseline 6.55 (SD 0.68); at 6 months 3.90 (SD 0.54); p<0.001	Both LNG-IUS and COCs decreased the pain and menstrual bleeding that is associated with adenomyosis.	Adequate sequence generation: **Low risk** Allocation concealment: **Low risk** Blinding: **High risk**

[51] Maximum dimension >100.0 mm or myometrial thickness >40.0 mm.
[52] Difference between groups analyzed by an analysis of covariance (ANCOVA), with the treatment group a fixed factor and the baseline score as a covariate using last observation carried forward.
[53] Assessed by the pain severity score, using a zero- to three- point verbal rating scale that defined pain severity according to limited ability to work and need for analgesics.

Study details	Participants	Intervention *(n)*	Methods	Results	Authors conclusion	Cochrane RoB tool
adenomyotic uteri: a randomized clinical trial. Contraception. 2015. 92:301-7. **Country** Egypt **Aim** This study compares the efficacy of LNG-IUS and a low-dose combined oral contraceptive in reducing adenomyosis-related pain and bleeding. **F/U** 6 months **Source of funding** Research grant obtained from the Assiut Medical School Grant's Office. Authors declared no COI.	of the Women's Health Hospital **Subgroup analysis** None **Inclusion criteria** Dysmenorrhoea and/or CPP; adenomyosis diagnosed by TVS; request for contraception for ≥6 months; aged 20 to 45 years; a local resident (to make follow-up easy). **Exclusion criteria** History of ectopic pregnancy, puerperal sepsis, PID; evidence of coagulopathy and/or abnormalities of uterine cavity; history of malignancy or histological evidence of endometrial hyperplasia; any adnexal abnormality on ultrasound; undiagnosed vaginal bleeding; any other contraindication to COCs.	**Group 2** low-dose COC *(n=31 randomised; n=28 analysed)*	proper insertion of the device immediately after insertion. The second group received COCs (Gynera; Bayer schering Helthcare), which included 30 ug of ethinyl estradiol and 75 ug of gestodene. Participants were instructed to use the COCs as prescribed (one pill every day for 21 days followed by a 1-week pill-free interval).	Intergroup comparisons: Baseline p=0.64; at 6 months p<0.001 **Patient satisfaction**[54] LNG-IUS: Baseline 7/31 women expressed satisfaction with different aspects of their lives; at 6 months 25/29 expressed overall satisfaction COC: Baseline 5/31 women expressed satisfaction with different aspects of their lives; at 6 months 18/28 expressed overall satisfaction **Study discontinuation** LNG-IUS: 2/31 (6.4%) COC: 3/31 (9.7%) **Discontinuation due to AE** LNG-IUS: 1/31 (3.2%) COC: 1/31 (3.2%)	However, LNG-IUS is more effective than the COCs in reducing pain and menstrual blood loss. This effect may be secondary to the decrease in uterine volume and the increase in blood flow resistance. We preferred to use cyclic rather than a continuous COC regimen because developing amenorrhoea is not always an acceptable option to women in our culture.	Incomplete outcome data addressed: **Some concerns** Free of selective reporting: **Low risk** Other bias: **Criteria for diagnosis of adenomyosis (using TVS) had a reported sensitivity between 86% and 86.67%** **Overall: Serious risk of bias and small sample size and short follow-up**

Abbreviations: AE, adverse event; COC, combined oral contraceptive; COI, conflict of interest; CPP, chronic pelvic pain; EAPP, endometriosis associated pelvic pain; F/U, follow up; Hb, haemoglobin; LNG–IUS, levonorgestrol-releasing intrauterine system; MRI, magnetic resonance imaging; PID, pelvic inflammatory disease; QoL, quality of life; SD, standard deviation, TVS, transvaginal sonography; VAS, visual analogue scale.

[54] Evaluated by three simple questions about the effect of pain and/or bleeding on physical health, sexual health and religious duties. Participants were considered to be satisfied if they denied that pain and/or bleeding affected any of the above three aspects of their life and were considered to be unsatisfied if any of them had been affected.

Clinical evidence profile

Endometriosis

Comparison 13: Combined oestrogen and progestogen pill ($Flexible_{MIB}$) versus placebo

Table 41 Evidence Profile Table: Hormonal medical treatments – Endometriosis – Comparison 13

No. of studies *References*	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients		Effect		Quality of evidence (GRADE)	Importance
						$Flexible_{MIB}$	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mean change in severest EAPP to 24 weeks – reported on VAS (0-100 mm)											
1 RCT *Harada et al 2017*	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	114	117	NR	LS MD: -26.3 (95% CI -31.6 to 20.9) Favours $Flexible_{MIB}$	Low	CRITICAL
Discontinuation due to AE											
1 RCT *Harada et al 2017*	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	NR	None	12/130 (9.2%)	2/128 (1.6%)	NR	Favours placebo	Low	CRITICAL
Patient satisfaction (highly/very highly satisfied)											
1 RCT *Harada et al 2017*	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	NR	None	43.1%	10.3%	NR	Favours $Flexible_{MIB}$	Low	IMPORTANT

Abbreviations: AE, adverse events; CI, confidence interval; EAPP, endometriosis associated pelvic pain; LS MD, least square mean difference, NR, not reported; RCT, randomised control trial; VAS, visual analogue scale

1. High rates of study discontinuation (20% in the intervention arm), no double blinding and insufficient information on allocation concealment.

Comparison 15: Progestogen (dienogest) versus placebo

Table 42 Evidence Profile Table: Hormonal medical treatments – Endometriosis – Comparison 15

No. of studies *References*	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients		Effect		Quality of evidence (GRADE)	Importance
						Dienogest	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mean change in EAPP from baseline to 24 weeks (VAS)											
1 RCT *Lang et al 2018*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	No serious imprecision	None	126	129	NR	LS MD: -24.54 mm (95% CI -29.93, - 19.15) Favours dienogest	Low	CRITICAL
Mean change in EAPP from baseline to 24 weeks (B&B)											
1 RCT *Lang et al 2018*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	NR	None	126	129	NR	MD: 1.7[3] Favours dienogest	Very low	CRITICAL
Proportion of responders (25% reduction in VAS) between baseline and 24 weeks											
1 RCT *Lang et al 2018*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	NR	None	68.3%	31.8%	NR	Favours dienogest	Low	CRITICAL
Proportion of responders (50% reduction in VAS) between baseline and 24 weeks											
1 RCT *Lang et al 2018*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	NR	None	60.3%	17.8%	NR	Favours dienogest	Low	CRITICAL
Proportion of responders (75% reduction in VAS) between baseline and 24 weeks											
1 RCT *Lang et al 2018*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	NR	None	43.7%	10.1%	NR	Favours dienogest	Low	CRITICAL
Mean change in QoL *physical component score* from baseline to 24 weeks (SF-36)											
1 RCT *Lang et al 2018*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	NR	None	126	129	NR	MD: 5.03[3]	Very low	CRITICAL
Mean change in QoL *mental component score* from baseline to 24 weeks (SF-36)											
1 RCT *Lang et al 2018*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	NR	None	126	129	NR	MD: 2.73[3]	Very low	CRITICAL

No. of studies *References*	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients		Effect		Quality of evidence (GRADE)	Importance
						Dienogest	Placebo	Relative (95% CI)	Absolute (95% CI)		
Treatment satisfaction (much/very much satisfied)											
1 RCT *Lang et al 2018*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	NR	None	95 (75.4%)	45 (34.9%)	NR	Favours dienogest	Low	IMPORTANT
Discontinuation due to AE											
1 RCT *Lang et al 2018*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	NR	None	2 (1.6%)	2 (1.6%)	NR	No difference	Low	CRITICAL

Abbreviations: AE, adverse events; B&B, Biberoglu and Behrman; CI, confidence interval; LS MD: least square mean difference; MD, mean difference; NR, not reported; QoL, quality of life; RCT, randomised control trial; SF-36, 36-item Short Form health survey; VAS, visual analogue scale.

1. Insufficient information on sequence generation and high risk of incomplete data addressed (14% study discontinuation).
2. Study conducted in Chinese women in China.
3. Calculated by evidence review team using summary data (mean change in dienogest group minus mean change in placebo group).

Comparison 16: Progestogen (Implanon) versus progestogen (Mirena)

Table 43 Evidence Profile Table: Hormonal medical treatments – Endometriosis – Comparison 16

No. of studies *References*	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients		Effect		Quality of evidence (GRADE)	Importance
						Implanon	Mirena	Relative (95% CI)	Absolute (95% CI)		
Change in noncyclical pelvic pain from baseline to 180 days – reported on VAS (0-100 mm)											
1 RCT *Carvalho et al 2018*	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision[2]	None	43	39	NR	MD: 0.1[3] No difference	Low	CRITICAL
Change in dysmenorrhoea from baseline to 180 days – reported on VAS (0-100 mm)											
1 RCT *Carvalho et al 2018*	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision[2]	None	43	39	NR	MD: 0.1 No difference	Low	CRITICAL
Change in HRQoL (EHP-30 questionnaire) from baseline to 180 days											
1 RCT *Carvalho et al 2018*	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	NR	None	43	39	NR	No statistical difference between groups	Low	CRITICAL

No. of studies *References*	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients		Effect		Quality of evidence (GRADE)	Importance
						Implanon	Mirena	Relative (95% CI)	Absolute (95% CI)		
Discontinuation due to AE											
1 RCT *Carvalho et al 2018*	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	NR	None	0/43 (0%)	0/39 (0%)	NR	NR No difference	Low	CRITICAL

Abbreviations: AE, adverse events; CI, confidence interval; EHP, Endometriosis Health Profile-5; HRQoL, health-related quality of life; MD: mean difference; NR, not reported; RCT, randomised control trial; VAS, visual analogue scale.

1. Open label trial; high rates of discontinuation (20%).
2. Relatively small confidence intervals for mean changes within groups.
3. Calculated by evidence review team using summary data (mean change in Implanon group subtract mean change in Mirena group)

Comparison 17: GnRH receptor antagonist (elagolix) versus placebo

Table 44 Evidence Profile Table: Hormonal medical treatments – Endometriosis – Comparison 17

No. of studies *References*	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients		Effect		Quality of evidence (GRADE)	Importance
						Elagolix	Placebo	Relative (95% CI)	Absolute (SE); (p-value)		
LS mean change in EAPP (NRS) from baseline to 3 months											
1 RCT *Taylor et al 2017* ***ELARIS EM I***	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	No serious imprecision	None	226 *150mg*	329	NR	-0.65 (SE 0.16); p<0.001 Favours elagolix	Low	CRITICAL
						213 *200mg*		NR	-1.30 (SE 0.16); p<0.001 Favours elagolix	Low	
1 RCT *Taylor et al 2017* ***ELARIS EM II***	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	No serious imprecision	None	204 *150mg*	312	NR	-0.57 (SE 0.16); p<0.001 Favours elagolix	Low	
						209 *200mg*		NR	-1.22 (SE 0.16); p<0.001 Favours elagolix	Low	
Clinically meaningful reduction in dysmenorrhoea and decreased or stable use of rescue analgesics at 3 months											
1 RCT *Taylor et al 2017* ***ELARIS EM I***	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	NR	None	46.4% *150mg:*	19.6%	NR	Favours elagolix	Low	CRITICAL
						75.8% 200mg		NR	Favours elagolix	Low	

No. of studies *References*	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients		Effect		Quality of evidence (GRADE)	Importance
						Elagolix	Placebo	Relative (95% CI)	Absolute (SE); (p-value)		
1 RCT *Taylor et al 2017* ***ELARIS EM II***	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	NR	None	43.4% 150*mg*	22.7%	NR	Favours elagolix	Low	
						72.4% *200mg*		NR	Favours elagolix	Low	
Clinically meaningful reduction in NMPP and decreased or stable use of rescue analgesics at 3 months											
1 RCT *Taylor et al 2017* ***ELARIS EM I***	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	NR	None	50.4% *150mg*	36.5%	NR	Favours elagolix	Low	CRITICAL
						54.5% *200mg*		NR	Favours elagolix	Low	
1 RCT *Taylor et al 2017* ***ELARIS EM II***	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	NR	None	49.8% 150*mg*	36.5%	NR	Favours elagolix	Low	
						57.8% *200mg*		NR	Favours elagolix	Low	
Discontinuation due to AE											
1 RCT *Taylor et al 2017* ***ELARIS EM I***	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	NR	None	16/249 (6.4%) *150mg*	22/374 (5.9%)	NR	NR	Low	CRITICAL
						23/248 (9.3%) *200mg*		NR	NR	Low	
1 RCT *Taylor et al 2017* ***ELARIS EM II***	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	NR	None	10/226 (4.4%) *150mg*	22/360 (6.1%)	NR	NR	Low	
						23/229 (10.2%) *200mg*		NR	NR	Low	

Abbreviations: AE, adverse events; CI, confidence interval; EAPP, endometriosis associated pelvic pain; MD: mean difference; NMPP, non-menstrual pelvic pain; NR, not reported; NRS, numerical rating scale; RCT, randomised control trial.

1. High dropout rates (>20%); insufficient information on blinding; selective reporting (NRS at 6 months not reported); short follow-up.
2. Elagolix is not TGA approved.

Comparison 18: GnRH receptor antagonist (opigolix 10mg) versus placebo

Table 45 Evidence Profile Table: Hormonal medical treatments – Endometriosis – Comparison 18

No. of studies *References*	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients		Effect		Quality of evidence (GRADE)	Importance
						Opigolix 10 mg/day	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mean difference in NRS Pain Score from baseline to 12 weeks (vs. placebo)											
1 RCT *D'Hooghe et al 2018*	Moderate risk of bias[1]	No serious inconsistency	Serious indirectness[2]	Serious imprecision[3]	None	90	88	NR	MD: -0.73 (95% CI: - 1.32 to - 0.13) Favours opigolix	Low	CRITICAL
Mean difference in NMPP (Modified B&B) from baseline to 12 weeks											
1 RCT *D'Hooghe et al 2018*	Moderate risk of bias[1]	No serious inconsistency	Serious indirectness[2]	Serious imprecision[3]	None	90	88	NR	MD: -1.01 (95% CI: - 1.17 to - 0.85) Favours opigolix	Low	CRITICAL
Mean difference in dysmenorrhoea (Modified B&B) from baseline to 12 weeks											
1 RCT *D'Hooghe et al 2018*	Moderate risk of bias[1]	No serious inconsistency	Serious indirectness[2]	Serious imprecision[3]	None	90	88	NR	MD: -1.53 (95% CI: - 1.73 to - 1.34) Favours opigolix	Low	CRITICAL
Discontinuation due to AE											
1 RCT *D'Hooghe et al 2018*	Moderate risk of bias[1]	No serious inconsistency	Serious indirectness[2]	NR	None	1/90 (1.1%)	0/88 (0%)	NR	NR	Low	CRITICAL

Abbreviations: AE, adverse events; B&B, Biberoglu and Behrman; CI, confidence interval; GnRH; Gonadotrophin-releasing hormone; MD, mean difference; NMPP, nonmenstrual pelvic pain, NR, not reported; NRS, numerical rating scale; RCT, randomised control trial.

1. Clinical practice may differ between countries; high rates of study discontinuation (>15%); short follow-up.
2. Opigolix is not yet TGA approved.
3. Large SE.

Endometriosis – hormonal medical treatment after surgery

Comparison 20: Progestogen (dienogest) versus GnRH agonist (leuprolide acetate)

Table 46 Evidence Profile Table: Hormonal medical treatments – Endometriosis – Comparison 20

No. of studies *References*	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients		Effect		Quality of evidence (GRADE)	Importance
						Dienogest	Leuprolide acetate	Relative	T test [3] (p-value)		
Mean pelvic pain at 12 weeks – reported on VAS (0-100 mm)											
1 RCT *Abdou et al 2018*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	No serious imprecision	None	101	96	NR	-1.377 (p=0.170) No difference	Low	CRITICAL
Mean back pain at 12 weeks – reported on VAS (0-100 mm)											
1 RCT *Abdou et al 2018*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	No serious imprecision	None	72	68	NR	-0.529 (p=0.597) No difference	Low	CRITICAL
Mean dyspareunia at 12 weeks – reported on VAS (0-100 mm)											
1 RCT *Abdou et al 2018*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	No serious imprecision	None	55	62	NR	-1.125 (p=0.263) No difference	Low	CRITICAL
Discontinuation due to abnormal uterine bleeding											
1 RCT *Abdou et al 2018*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	No serious imprecision	None	0/130 (0%)	0/131 (0%)	NR	NR No difference	Low	CRITICAL

Abbreviations: AE, adverse events; CI, confidence interval; GnRH; Gonadotrophin-releasing hormone; NR, not reported; RCT, randomised control trial; VAS, visual analogue scale.

1. No blinding and incomplete outcome data; short follow-up.
2. Study conducted in Egypt.
3. Percentages in groups were compared by Chi-square test and differences between parametric quantitative independent groups by t test in pairs by paired t.

Adenomyosis

Comparison 1: Progestogen (dienogest) versus placebo

Table 47 Evidence Profile Table: Hormonal medical treatments – Adenomyosis – Comparison 1

No. of studies *References*	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients		Effect		Quality of evidence (GRADE)	Importance
						Dienogest	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mean change in EAPP from baseline to 16 weeks – reported on VAS (0-100 mm)											
1 RCT *Osuga et al 2017*	Moderate risk of bias	No serious inconsistency	Serious indirectness[1]	Serious imprecision[2]	None	34	33	NR	MD: 37.8[3] Favours dienogest	Low	CRITICAL
Mean change in pain score from baseline to 16 weeks[3]											
1 RCT *Osuga et al 2017*	Moderate risk of bias	No serious inconsistency	Serious indirectness[1]	Serious imprecision[2]	None	34	33	NR	MD: 2.4[3] Favours dienogest	Low	CRITICAL
Mean change in pain severity score from baseline to 16 weeks											
1 RCT *Osuga et al 2017*	Moderate risk of bias	No serious inconsistency	Serious indirectness[1]	Serious imprecision[2]	None	34	33	NR	MD: 12.5[3] Favours dienogest	Low	CRITICAL
Mean change in QoL (SF-36) from baseline to 16 weeks											
1 RCT *Osuga et al 2017*	Moderate risk of bias	No serious inconsistency	Serious indirectness[1]	Serious imprecision[2]	None	34	33	NR	Significant only for role physical and bodily pain Favours dienogest	Low	CRITICAL
Discontinuation due to AE											
1 RCT *Osuga et al 2017*	Moderate risk of bias	No serious inconsistency	Serious indirectness[1]	NR	None	1/34 (2.9%)	1/33 (3.0%)	NR	NR	Low	CRITICAL

Abbreviations: AE, adverse events; CI, confidence interval; EAPP, endometriosis associated pelvic pain; NR, not reported; QoL, quality of life; RCT, randomised control trial; SF-36, 36-Item Short Form Survey; VAS, visual analogue scale.

1. Patients with adenomyosis may also have endometriosis. Unclear diagnostic criteria for adenomyosis. Short follow-up. Study conducted in Japan.
2. Large SD and small sample size.
3. Calculated by evidence review team using summary data (mean change in dienogest group minus mean change in placebo group).

Comparison 2: Progestogen (Mirena) versus combined oestrogen/progestogen (low dose combined oral contraceptive)

Table 48 Evidence Profile Table: Hormonal medical treatments – Adenomyosis – Comparison 2

No. of studies *References*	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients		Effect		Quality of evidence (GRADE)	Importance
						LNG-IUS (Mirena)	Low dose COC	Relative (95% CI)	Absolute (95% CI)		
Mean pelvic pain – reported on VAS (0-100 mm)											
1 RCT *Shaaban et al 2017*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	Serious imprecision[3]	None	29	31	NR	MD: 1.9[4] Favours LNG-IUS	Very low	CRITICAL
Discontinuation due to AE											
1 RCT *Shaaban et al 2017*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	Serious imprecision[3]	None	1/31 (3.2%)	1/31 (3.2%)	NR	No difference	Very low	CRITICAL
Patient satisfaction with different aspects of their lives at baseline											
1 RCT *Shaaban et al 2017*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	Serious imprecision[3]	None	7/31 (22.6%)	5/31 (16.1%)	NR	NR	Very low	IMPORTANT
Patient satisfaction with different aspects of their lives at 6 months											
1 RCT *Shaaban et al 2017*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	Serious imprecision[3]	None	25/29 (86.2%)	18/28 (64.3%)	NR	NR	Very low	IMPORTANT

Abbreviations: AE, adverse events; CI, confidence interval; COC, combined oral contraceptive; NR, not reported; RCT, randomised control trial; VAS, visual analogue scale.

1. No double blinding and some concerns with dropout rates.
2. Study conducted in Egypt.
3. Small sample size.
4. Calculated by evidence review team using summary data (mean change in dienogest group minus mean change in placebo group). Statistical analysis represents outcomes at 6 months rather than change from baseline.

Clinical evidence statements

Endometriosis

Comparison 13: Combined oestrogen and progestogen pill (Flexible$_{MIB}$) versus placebo

Harada et al 2017 (Japan) – Overall serious risk of bias

Pelvic pain

Low quality evidence from 1 RCT (n=231) demonstrated a clinically significant beneficial effect of combined oestrogen and progestogen (Flexible$_{MIB}$; 20 ug ethinylestradiol and 3 mg drospirenone, once daily) compared with placebo in the reduction of severest pelvic pain (measured using VAS) at 24 weeks after starting treatment.

Comparison 14: Combined oestrogen and progestogen pill (Flexible$_{MIB}$) versus progestogen (dienogest)

Harada et al 2017 (Japan) – Overall very serious risk of bias

Pelvic pain

Very low quality evidence from 1 RCT (n=183) demonstrated a clinically significant beneficial effect of dienogest (1 mg twice daily) compared with combined oestrogen and progestogen (Flexible$_{MIB}$; 20 ug ethinylestradiol and 3 mg drospirenone, once daily) in the reduction of severest pelvic pain (measured using VAS) at 24 weeks after starting treatment.

Comparison 15: Progestogen (dienogest) versus placebo

Lang et al 2018 (China) – Overall serious risk of bias

Pelvic pain

Low quality evidence from 1 RCT (n=255) demonstrated a clinically significant beneficial effect of dienogest (2 mg once daily) compared with placebo in the reduction of pelvic pain (measured using VAS) at 24 weeks after starting treatment.

Quality of life

Very low quality evidence from 1 RCT (n=255) demonstrated a statistically significant beneficial effect of dienogest (2 mg once daily) compared with placebo on quality of life (measured using SF-36) at 24 weeks after starting treatment.

Comparison 16: Progestogen (Implanon) versus progestogen (Mirena)

Carvalho et al 2018 (Brazil) – Overall serious risk of bias

Noncyclical pelvic pain

Low quality evidence from 1 RCT (n=82) found no clinically significant difference between ENG-releasing contraceptive implant (Implanon) and LNG-IUS (Mirena) on noncyclical pelvic pain (measured using VAS) at 180 days after starting treatment.

Dysmenorrhoea

Low quality evidence from 1 RCT (n=82) found no clinically significant difference between ENG-releasing contraceptive implant (Implanon) and LNG-IUS (Mirena) on dysmenorrhoea (measured using VAS) at 180 days after starting treatment.

Quality of life

Low quality evidence from 1 RCT (n=82) found no clinically significant difference between ENG-releasing contraceptive implant (Implanon) and LNG-IUS (Mirena) on quality of life (measured using EHP-30) at 180 days after starting treatment.

Comparison 17: GnRH receptor antagonist (elagolix) versus placebo

Taylor et al 2017 (5 continents, including Canada and US) – Overall serious risk of bias

Note: Elagolix is not TGA-approved

Pelvic pain

Low quality evidence from 2 RCTs (n=1,686) demonstrated a statistically significant beneficial effect of elagolix (150 mg once daily and 200 mg twice daily) compared with placebo in the reduction of pelvic pain (measured using NRS) at 3 months after starting treatment.

Comparison 18: GnRH receptor antagonist (opigolix) versus placebo

D'Hooghe et al 2019 (Europe and Japan) – Overall moderate risk of bias

Note: Opigolix is not TGA-approved

Pelvic pain

Low quality evidence from 1 RCT (n=448) demonstrated a statistically significant beneficial effect of opigolix (10 mg once daily) compared with placebo in the reduction of overall pelvic pain (measured using NRS) at 12 weeks after starting treatment. A *statistically significant* beneficial effect was not seen for the other opigolix doses investigated (3 mg, 5 mg, and 15 mg once daily).

Low quality evidence from 1 RCT (n=448) demonstrated a statistically significant beneficial effect of opigolix (3 mg, 5 mg, 10 mg and 15 mg once daily) compared with placebo in the reduction of dysmenorrhoea (measured using NRS) at 12 weeks after starting treatment. A *statistically significant* beneficial effect of opigolix was also demonstrated for all tested doses compared with placebo using the Biberoglu and Behrman scale.

Low quality evidence from 1 RCT (n=448) found no statistically significant beneficial effect of opigolix (3 mg, 5 mg, 10 mg and 15 mg once daily) compared with placebo on nonmenstrual pelvic pain (measured using NRS) at 12 weeks after starting treatment. However, a *statistically significant* beneficial effect of opigolix (10 mg and 15 mg) was demonstrated when nonmenstrual pelvic pain was measured using the Biberoglu and Behrman scale.

Comparison 19: GnRH receptor antagonist (opigolix) versus GnRH agonist (leuprorelin acetate)

D'Hooghe et al 2019 (Europe and Japan) – Serious risk of bias

Note: Opigolix is not TGA-approved

No statistical analyses reported for this comparison but leuprorelin showed a larger pain reduction than opigolix.

Endometriosis – hormonal medical treatment after surgery

Comparison 20: Progestogen (dienogest) versus GnRH agonist (leuprolide acetate) after surgery

Abdou et al 2018 (Egypt) – Overall serious risk of bias

Pain scores

Low quality evidence from 1 trial (n=197 to 117) found no significant difference between dienogest (2 mg daily) compared with leuprolide acetate (3.75 mg/4 weeks) in the reduction of pelvic pain, back pain and dyspareunia (measured using VAS) at 12 weeks after starting treatment.

Adenomyosis

Comparison 1: Progestogen versus placebo

Osuga et al 2017 (Japan) – Overall moderate risk of bias

Pelvic Pain

Low quality evidence from 1 trial (n=67) found a clinically significant beneficial effect of dienogest (1 mg twice daily) compared with placebo in the reduction of pelvic pain (measured using VAS) at 16 weeks after starting treatment.

Comparison 2: Progestogen versus combined oestrogen/progestogen

Shaaban et al 2015 (Egypt) – Overall serious risk of bias

Pelvic pain

Very low quality evidence from 1 trial (n=60) found a clinically significant beneficial effect of LNG-IUS (Mirena) compared with a cyclic regimen of low dose combined oral contraceptive (30 ug ethinyl estradiol and 75 ug gestodene) in the reduction of pelvic pain (measured using VAS) at 6 months after starting treatment.

Q8 – Alternatives to pharmacological and surgical management

In people with endometriosis or adenomyosis, what alternatives to pharmacological and surgical management are effective for managing endometriosis- or adenomyosis- associated pain?

Description of clinical evidence

The literature search date was **16 October 2019**.

Clinical evidence is summarised by intervention type, as classified in the Research Protocol:

- Behavioural/psychological medicine – includes cognitive behavioural therapy; relaxation techniques' pain management programs; pain management physiotherapy; pain management psychology; expert patient program; hypnosis; psychosexual therapy; biofeedback
- Lifestyle medicine – includes exercise [e.g. yoga, Pilates, tai chi); meditation; mindfulness; dietary therapies [gluten free; dairy free; vegetarian; FODMAP diet]
- Physical methods – includes acupuncture; transcutaneous electrical nerve stimulation [TENS]; manual and physical therapy; massage [e.g. shiatsu]; osteopathy; chiropractic treatment; reflexology
- Other – includes dietary supplements; herbal medicine (e.g. Chinese Herbal Medicine [CHM]); naturopathy; homeopathic therapy; ayurvedic therapies; aromatherapy.

Endometriosis

Behavioural/psychological medicine

Four new relevant SRs were identified:

- Psychological and mind-body interventions (Evans et al 2019)
- Self-management (O'Hara et al 2019)
- Psychological interventions (Van Niekerk et al 2019)
- Behavioural, cognitive, and emotional coping strategies (Zarbo et al 2018).

Three of the four SRs (Evans et al 2019; O'Hara et al 2019; van Niekerk et al 2019) identified one relevant RCT not already captured in the NICE Guideline: Hatha yoga (Goncalves et al 2017), which is captured in the current report under 'Lifestyle medicine' (see below).

No new relevant RCTs were identified relating to behavioural/psychological medicine.

Lifestyle medicine

No new relevant SRs were identified.

One new relevant RCT was identified:

- Hatha yoga (Goncalves et al 2017)

Physical methods

One new relevant SR was identified:

- acupuncture (Xu et al 2017) – no relevant RCTs[55]

One new relevant RCT was identified:

- meridian balance method electro-acupuncture (Chong et al 2018)[56]

Other interventions

One new relevant SR was identified:

- micronised palmitoylethanolamide (PEA)/transpolydatin combination (Indraccolo et al 2016) – included **one relevant RCT**
    - micronised PEA/transpolydatin (Cobellis et al 2011)

One new RCT was identified in the literature search:

- homeopathy (Teixeira et al 2017)

Three new relevant RCTs were identified by EEWG members:

- vitamin D (Almassinokiani et al 2016)[56]
- antioxidant vitamins (Vitamin C plus Vitamin E combination) (Santanam et al 2013)[56]
- melatonin (Schwertner et al 2013)[56]

A fourth RCT identified by an EEWG member was excluded because it investigated the use of resveratrol as an adjuvant to the monophasic contraceptive pill (wrong comparator; Mendes da Silva et al 2017).

Complementary treatments, in general

The literature search identified one broad SR that aimed to identify RCTs of "resources, methods, and/or complementary treatments to alleviate the pain symptoms of women with endometriosis and the clinical effects of treatment" (Mira et al 2018). Eight RCTs were included, three of which related to exercise, three related to acupuncture, one related to acupuncture-applied TENS, and one related to Hatha yoga. One of the eight RCTs was published after the NICE guideline literature search date: Hatha yoga (Goncalves et al 2017). This RCT is included below.

Adenomyosis

No relevant studies were identified.

[55] Nine of the ten included RCTs were in Chinese language or were theses/dissertations. One RCT from the US was published in 2008.
[56] This reference was not identified in the literature search but was identified by the EEWG.

Summary of included studies

Endometriosis

Behavioural/psychological medicine

No new relevant studies were identified.

Physical methods

One new RCT was included: electro-acupuncture with traditional Chinese medicine health consultation (Chong et al 2018). This trial is summarised below.

Table 49 Evidence Summary: Alternatives to pharmacological and surgical management – Physical methods

Study details	Participants	Intervention *(n)*	Methods	Results	Authors conclusion	Cochrane RoB tool
Full citation Chong, OT, Critchley HOD, Williams LJ, Haraldsdottir E, Horne AW, Fallon M. The impact of meridian balance method electro-acupuncture treatment on chronic pelvic pain in women: a three-armed randomised controlled feasibility study using a mixed-methods approach. British Journal of Pain. 2018. 12:238-249. **Country** United Kingdom **Aim** To evaluate the feasibility of a future large-scale RCT to determine the effectiveness of the meridian BMEA treatment for CPP in women. **F/U** 12 weeks **Source of funding** Morag Robinson Legacy and the Alexander Dykes Fund	**Population** Women with CPP; 21/30 (70%) study participants had endometriosis[57] **Setting** Attended the Edinburgh Centre for Pelvic Pain and Endometriosis Care and Treatment Centre (EXPPECT Centre), Edinburgh, UK. **Subgroup analysis** NA **Inclusion criteria** CPP longer than 6-month duration; average pain score on an NRS of at least 4 out of 10 (0–10) in the previous week; women aged 18 years or over; able and willing to comply with the interventions. **Exclusion criteria** Malignancy; severe bleeding disorders; taking regular anti-coagulant; severe needle phobia; pacemaker in situ; history of seizures; treatment with EA and meridian BM within the last 6 months; moderate to severe psychiatric illness and under the care of a psychiatrist.	**Group 1**: EA, combined with TCHC *(n=10)* **Group 2**: TCHC *(n=10)* **Group 3**: Western medicine *(n=10)*	**EA + TCHC** The step-by-step individualised and systematic acupuncture point have been described in detail by Chong et al.[58] **Western Medicine** NHS standard care	**Mean change in NRS pelvic pain at 12 weeks** Group 1: -0.9, SD 2.0 Group 2: -0.2, SD 2.1 Group 3: -1.1, SD 1.8 **BPI pelvic pain at 12 weeks** Group 1: -0.2, SD 2.7 Group 2: -0.6, SD 1.9 Group 3: -1.0, SD 1.8 **Retention rates (percentage completed and returned follow-up questionnaires at Weeks 4, 8, 12)** Group 1: 80% (95% CI: 74 to 96) Group 2: 53% (95% CI: 36 to 70) Group 3: 87% (95% CI: 63 to 90)	Qualitative data suggested a favourable trial experience in groups 1 and 3. Group 2 retention rate was problematic. Significant modifications to our pilot study design are necessary before we can move forward to a full large-scale phase 3 RCT to evaluate the effectiveness of the meridian BMEA treatment for CPP in women.	Adequate sequence generation: **Low risk** Allocation concealment: **Low risk** Blinding: **High risk** Incomplete outcome data addressed: **Insufficient information** Free of selective reporting: **Low risk** Other bias: **Small pilot study with low attendance, low rate of questionnaire return and high missing data** **<u>Overall</u>: Very serious risk of bias**

Abbreviations: BM, meridian balance method; BMEA, balanced method electro-acupuncture; BPI, Brief Pain Inventory; CI, confidence interval; CPP, chronic pelvic pain; EA, electro-acupuncture; F/U, follow-up; NA, not assessed; NHS, National Health Service; NRS, numeric rating scale; RCT, randomised controlled trial; RoB, risk of bias; SD, standard deviation; TCHC, traditional Chinese medicine health consultation; VAS, visual analogue scale.

Lifestyle medicine

One new RCT was included: Hatha yoga (Goncalves et al 2017). This trial is summarised below.

[57] Details of how endometriosis was diagnosed were not provided.

[58] Chong OT, Critchley HO, Horne AW, et al. The BMEA study: the impact of meridian balanced method electroacupuncture on women with chronic pelvic pain – a three-arm randomised controlled pilot study using a mixed-methods approach. BMJ Open 2015; 5: e008621

Table 50 Evidence Summary: Alternatives to pharmacological and surgical management – Lifestyle medicine

Study details	Participants	Intervention *(n)*	Methods	Results	Authors conclusion	Cochrane RoB tool
Full citation Goncalves AV, Barros NF, Bahamondes L. The practice of Hatha yoga for the treatment of pain associated with endometriosis. Journal of Alternative and Complementary Medicine. 2017. 23:45-52. **Country** Brazil **Aim** To compare CPP, menstrual patterns, and QoL in two groups of women with endometriosis: those who did and those who did not participate in a specific 8-week yoga intervention. **F/U** 8 weeks **Source of funding** Not reported	**Population** Women with endometriosis-associated CPP **Setting** Endometriosis outpatient clinic and outpatient physical therapy clinic of the Department of Obstetrics and Gynecology, University of Campinas Medical School. **Subgroups** NA **Inclusion criteria** Women aged 18–50 years old, presented with a confirmed diagnosis of endometriosis; CPP with a score >4 measured by VAS; already received some type of treatment for endometriosis (e.g. hormonal therapy, laparoscopy, etc.); available to attend the clinic to practice yoga twice a week for 8 weeks. **Exclusion criteria** Pregnant; having recent physical trauma; exercising more than three times a week.	**Group 1**: Hatha Yoga *(n=28)* **Group 2**: Standard treatment given to every endometriosis patient at the clinic: medication and/or one individual physical therapy session a week *(n=12)*[59]	**Hatha Yoga** 2-hour sessions held at the clinic twice a week. Sessions consisted of 30 min conversation and interaction among participants; 10 min of initial physical and psychological relaxation, with intonation of mantras and body awareness; 60 min of asanas (hatha yoga postures with 5–10 breathing exercises); 10 min of exercises for physical and psychological relaxation that included meditation, breathing techniques, and chanted mantras; and a final 10 min where women commented on the session and organised the room in which the class took place.	**Weekly mean pelvic pain (VAS)** Yoga: 4.1; 4.0; 4.3; 3.9; 4.0; 3.2; 3.3; 3.8 Control 5.3; 5.2; 4.8; 5.5; 5.9; 6.8; 6; 6.5 (significantly lower in yoga compared with control group; p not specified) **EHP 30 central questionnaire, difference between groups over time** pain (p=0.0046), control and powerlessness (p=0.0006), emotional wellbeing (p=0.0009), social support (p=1228), self image (p=0.0087) **Discontinuation at 8 weeks** Yoga: 12/28 (43%) No yoga: 0/12 (0%)	Yoga practice was associated with a reduction in levels of CPP and an improvement in QoL in women with endometriosis. A strength of this study is that prior to yoga sessions, women had time to talk among themselves and with the yoga instructor who, when possible, was able to clarify some of the questions the participants had regarding treatment, diagnostic procedures, or other issues. Apparently, it contrasted with the kind of attention they received in the doctor's office.	Adequate sequence generation: **Low risk** Allocation concealment: **Low risk** Blinding: **High risk** Incomplete outcome data addressed: **Low risk** Free of selective reporting: **Low risk** Other bias: **imbalance in study arm allocation; baseline imbalance in schooling and professional activity; high discontinuation in yoga arm** **<u>Overall</u>: Very serious risk of bias**

Abbreviations: CPP, chronic pelvic pain; EHP, Endometriosis Health Profile; F/U, follow-up; NA, not assessed; QoL, quality of life; RoB, risk of bias; VAS, visual analogue scale.

Other interventions

Five new RCTs were identified. Four relate to dietary supplements: vitamin D (Almassinokiani et al 2016); vitamin C + E (Santanam et al 2013); melatonin (Schwertner et al 2013); PEA/transpolydatin combination (Cobellis et al 2011). One relates to homeopathy: Teixeira et al 2017. These trials are summarised below.

[59] Randomisation was computer-generated in a proportion 3:1.

Table 51 Evidence Summary: Alternatives to pharmacological and surgical management – Other interventions

Study details	Participants	Intervention *(n)*	Methods	Results	Author conclusion	Cochrane RoB tool/ comments
Full citation Almassinokiani F, Khodaverdi S, Solaymani-Dodaran M, Akbari P, Pazouki A. Effects of vitamin D on endometriosis-related pain: A double-blind clinical trial. Medical science monitor: international medical journal of experimental and clinical research. 2016. 22:4960. **Country** Iran **Aim** To explore the relationship between vitamin D and endometriosis in a double-blind, RCT looking at the effect of vitamin D supplementation on cessation of pain in proven endometriosis after laparoscopic diagnosis and treatment. **F/U** 24 weeks **Source of funding** Iran University of Medical Sciences	**Population** Women with endometriosis-related pain 8 weeks after ablative surgery Severity of endometriosis: 3% minimal; 5% mild; 45% was moderate; 47% was severe **Setting** A single tertiary university hospital **Subgroup analysis** NA **Inclusion criteria** Women aged 15–40 years with proven endometriosis by laparoscopy and a VAS test score of 3 or more for dysmenorrhoea and/or pelvic pain at second menses after operative laparoscopy. **Exclusion criteria** Patients with vitamin D treatment in the last 6 months prior to surgery; known systemic diseases (e.g. hypertension, diabetes, coronary, renal, and hepatic diseases); known malignancy; menopausal women; hormonal treatment, including OCP, in the last 6 months.	**Group 1**: Vitamin D *(n=19)* **Group 2**: Placebo *(n=20)*	**Vitamin D** Oral vitamin D3 (50 000 IU/weekly) for 12 weeks **Placebo** 1 daily capsule of placebo pill	**VAS pelvic pain before laparoscopy** Vitamin D: 4.05 (SD 3.45) Placebo: 4.82 (SD 4.1) p=0.513 **VAS pelvic pain 24 weeks after laparoscopy** Vitamin D: 0.84 (SD 1.74) Placebo: 0.68 (SD 1.70) p=0.24	Further clinical trials are needed on the role of vitamin D treatment for endometriosis-related pain. Future studies should assess the serum levels of vitamin D before enrolling study subjects, and those with vitamin D deficiency should be excluded. Clinical trials with larger sample sizes will be able to produce more reliable results.	Adequate sequence generation: **Low risk** Allocation concealment: **Insufficient information** Blinding: **High risk** Incomplete outcome data addressed: **Low risk** Free of selective reporting: **Low risk** Other bias: **High percentage of the Iranian population may have had a vitamin D deficiency, which may have affected the results.** *Intervention was given after ablative surgery for endometriosis.* **Overall: Serious risk of bias**

Study details	Participants	Intervention *(n)*	Methods	Results	Author conclusion	Cochrane RoB tool/ comments
Full citation Santanam N, Kavtaradze N, Murphy A, Dominguez C, Parthasarathy S. Antioxidant supplementation reduces endometriosis-related pelvic pain in humans. Translational Research. 2013. 161:189-195. **Country** United States **Aim** To assess whether antioxidant supplementation would ameliorate endometriosis associated symptoms. **F/U** 8 weeks **Source of funding** NIH – National Institute of Child Health and Human Development funding. None of the authors claimed to have any financial or personal relationship with any organisations that would potentially influence the research.	**Population** Women with pelvic pain and history of endometriosis and/or infertility **Setting** Recruited from Emory Clinic and Crawford Long Hospital, affiliated to Emory University School of Medicine, Atlanta. **Subgroup analysis** NA **Inclusion criteria** Women aged 19–41 years with pelvic pain and history of endometriosis and/or infertility.[60] **Exclusion criteria** Not reported	**Group A**: Vitamin C + vitamin E *(n=46)* **Group B**: Placebo *(n=13)*[61]	**Antioxidant supplementation** Vitamin C (1000 mg; 2 tablets of 500 mg each) + vitamin E (1200 IU; 3 capsules of 400 mg each) daily for eight weeks prior to surgery No pre-treatment with other medications were given a week before or during the antioxidant supplementation **Placebo** One placebo pill daily for eight weeks prior to surgery	**'Everyday pain' at 8 weeks** Group A: 43% (p=0.0055) had a decrease; 52% had no change; 0.09% did not experience 'everyday pain'; 5% had an increase Group B:: no changes in 'everyday pain'	Though, the major limitation of our study is the patient number, the study does suggest that antioxidant vitamins are efficacious in decreasing CPP in women with endometriosis. Our study also suggested that natural antioxidants such as vitamin E and C at low doses, are highly efficient alternative therapy to relieve CPP in women with endometriosis. The current study also provided "in vivo" evidence for our global hypothesis that endometriosis is a disease of oxidative stress.	Adequate sequence generation: **insufficient information** Allocation concealment: **insufficient information** Blinding: **insufficient information** Incomplete outcome data addressed: **Low risk** Free of selective reporting: **Low risk** Other bias: **large imbalance in random allocation** *Study population may contain women without endometriosis (infertility unrelated to endometriosis).* **Overall: Very serious risk of bias**

[60] The actual number of participants with endometriosis is not reported in the publication.
[61] The reason for the imbalance in study group size is not explained in the publication.

Study details	Participants	Intervention *(n)*	Methods	Results	Author conclusion	Cochrane RoB tool/ comments
Full citation Schwertner A, Conceição Dos Santos CC, Dalferth Costa G, Deitos A, De Souza A, Custodio de Sousa IC, Torres ILS, da Cunha Filho JSL, Caumo W. Efficacy of melatonin in the treatment of endometriosis: A phase II, randomized, double-blind, placebo-controlled trial. Pain. 2013. 154:874-881. **Country** Brazil **Aim** To test the hypothesis that melatonin would be more effective than a placebo for the treatment of endometriosis associated CPP. **F/U** 8 weeks **Source of funding** Brazilian agencies: Committee for the Development of Higher Education Personnel – CAPES – PNPD/CAPES (grants to I.C.C. Souza; A. Deitos) and material support; National Council for Scientific and Technological Development – CNPq (grants to Dr. I.L.S. Torres, Dr. W. Caumo); Postgraduate Program in Medical Sciences at the School of Medicine of the Federal University of Rio Grande do Sul (material support)	**Population** Endometriosis-associated CPP **Setting** Recruitment from gynecology outpatient clinic at the Hospital de Clínicas de Porto Alegre and by newspaper publicity **Subgroup analysis** NA **Inclusion criteria** Patients with endometriosis confirmed by laparoscopic surgery (stage 1 - 4); between 18 and 45 years old; CPP and/or dyspareunia defined as a moderate-to-severe pain intensity lasting for more than 6 months; pain scores on a categorical scale (0 to 10) equal to or higher than 4 and requiring regular analgesic use. **Exclusion criteria** Non-gynecologic causes of pelvic pain; diagnosed malignancies, uterine myomas, ovarian cysts, IPD; pregnancy; history of neurologic or oncologic disease, IHD, kidney or hepatic insufficiency; regular intake of antidepressants or anticonvulsants that could not be discontinued at least 15 days before study start; history of alcohol or substance abuse in the past 6 months; undergoing hormonal therapy or had irregular cycles.	**Group 1**: Melatonin *(n=20)* **Group 2**: Placebo *(20)*	**Melatonin** 10 mg melatonin tablets (Sigma Chemical, Germany) **Placebo** Identical characteristics with placebo pill	**Adjusted MD in worst pain in last 24 hours at 8 weeks (VAS)** Adjusted MD: 1.80 (95% CI 0.59, 1.97) Relative change[62]: 39.30 (95% CI 12.88, 43.01) p<0.001 **Adjusted MD in pain during menstrual period at 8 weeks (VAS)** 2.6 (95% CI 0.38, 1.71) p<0.001 **Adjusted MD in pain during intercourse at 8 weeks (VAS)** 1.40 (95% CI 0.42, 1.49) p<0.001 **Study withdrawal due to treatment inefficacy** Melatonin: 3/20 (15%) Placebo: 1/20 (5%) **Relative risk of analgesic use during treatment period** 1.80 (95% CO 1.61, 2.08) Melatonin: 22.9% Placebo: 42.2% **Adjusted mean difference in sleep quality (VASQS)** 1.1 (95% CI 0.11, 1.39) Melatonin: 6.08 (SD 1.42) Placebo: 4.98 (SD 1.51)	The oral consumption of 10 mg/day of melatonin was associated with significant improvements in endometriosis-associated CPP and other efficacy measures. Melatonin reduced pain scores, lowered analgesic use, and improved sleep quality. Overall, melatonin may represent an effective and well-tolerated treatment for the painful symptoms of endometriosis. ….additional research with a larger number of patients is needed to more widely assess the potential benefits of melatonin in various clinical settings, and future studies are required before definitive conclusions regarding melatonin and pain treatment can be made.	Adequate sequence generation: **Low risk** Allocation concealment: **Low risk** Blinding: **Low risk** Incomplete outcome data addressed: **Low risk** Free of selective reporting: **Low risk** Other bias: **None identified** *Improvement in pain may have been due to improvement in sleep.* *Australian PI for melatonin (CIRCADIN) prolonged release capsules: Indicated for short term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over. Recommended daily dose is 2 mg once daily, continued for up to 13 weeks.* *Safety of the high dose of melatonin (adverse events) was not a study outcome.* **Overall: Small study using a high dose of melatonin but no serious risk of bias**

[62] Relative change = adjusted mean difference/adjusted placebo mean x 100%

Study details	Participants	Intervention *(n)*	Methods	Results	Author conclusion	Cochrane RoB tool/ comments
Full citation Cobellis L, Castaldi MA, Giordano V, Trabucco E, De Franciscis P, Torella M, Colacurci N. Effectiveness of the association micronized N-Palmitoylethanolamine (PEA)–transpolydatin in the treatment of chronic pelvic pain related to endometriosis after laparoscopic assessment: a pilot study. European Journal of Obstetrics and Gynecology. 2011. 158:82-86. **Country** Italy **Aim** To evaluate the effectiveness of the association between PEA and transpolydatin in the management of CPP related to endometriosis. **F/U** 3 months **Source of funding** Not reported	**Population** Women who have had first-line laparoscopic conservative surgery. All patients had minimal or mild endometriosis (Stage I or II). **Setting** Outpatient Division of Endometriosis Care, Department of Gynaecology, Obstetric and Reproductive Science **Subgroup analysis** NA **Inclusion criteria** Women between 24 and 41 years of age; diagnosis of endometriosis made according to the ESHRE guideline for the diagnosis and treatment of endometriosis; submitted to a first line laparoscopic conservative surgery. **Exclusion criteria** Use of oral contraceptives 3 months prior to laparoscopic surgery.	**Group A**: Laparoscopic surgery plus N-Palmitoylethanolamine–transpolydation *(n=21)* **Group B**: Laparoscopic surgery plus placebo *(n=20)* **Group C**: Laparoscopic surgery plus Celecoxib *(n=20)*	**PEA-transpolydatin** 400 mg + 40 mg twice a day for 3 months **Placebo** Same as intervention but lacking active ingredients **Celecoxib** Single course 200 mg twice a day for 7 consecutive days	**Change in median VAS pelvic pain from baseline (before laparoscopic conservative surgery) to 3 months after *(approx. from graph)*** Group A: -5.3 Group B: -2.4 Group C: -6.3 p<0.001 (Kruskal-Wallis test) **Satisfaction with treatment** Group A: 16/21 (76%) very satisfied or satisfied; 4/21 (19%) uncertain; 1/21 (5%) dissatisfied Group B: 8/20 (40%) very satisfied or satisfied; 5/20 (25%) uncertain; 7/20 (35%) dissatisfied or very dissatisfied Group C: 14/20 (70%) very satisfied or satisfied; 3/20 (15%) uncertain; 3/20 (15%) dissatisfied or very dissatisfied **Recurrence (confirmed by rise in CA-125 values and by TVUS)** Group A: 1/21 Group B: 2/20 Group C: 0/20	Micronised PEA + polydatin showed an efficacy in pain control higher than the placebo, which showed an efficacy in the reduction of pain. On the other hand, Celecoxib resulted more effective in pain control either than PEA-polydatin or placebo. Our pilot study assesses that the association between micronised PEA and transpolydatin seems to be effective in the management of pelvic pain related to endometriosis after laparoscopy. Additionally, this safe association shows an optimal control of pain and could be used in patients who are unable to receive other therapies.	Adequate sequence generation: **Low risk** Allocation concealment: **Low risk** Blinding: **High risk** (Celecoxib) Incomplete outcome data addressed: **Low risk** Free of selective reporting: **Low risk** Other bias: **none identified** *Laparoscopic surgical procedure could have contributed to the reduction in pelvic pain.* *Australian PI for celecoxib: Indicated for primary dysmenorrhoea. Recommended dose is 400 mg as a single dose or divided on the first day followed by 200 mg OD on subsequent days. Patients may be instructed to take an additional dose of 200 mg on any given day, if needed. The maximum recommended treatment duration is 5 days.* **<u>Overall</u>: Small sample size and serious risk of bias**

Study details	Participants	Intervention *(n)*	Methods	Results	Author conclusion	Cochrane RoB tool/ comments
Full citation Teixeira MZ, Podgaec S, Baracat EC. Potentized estrogen in homeopathic treatment of endometriosis-associated pelvic pain: A 24-week, randomized, double-blind, placebo-controlled study. European Journal of Obstetrics, Gynecology, & Reproductive Biology. 2017. 211:48-55. **Country** Brazil **Aim** To evaluate the efficacy and safety of potentized estrogen compared to placebo in homeopathic treatment of endometriosis-associated pelvic pain. **F/U** 24 weeks **Source of funding** None (postdoctoral research project)	**Population** Women with pelvic pain associated with deep endometriosis lesions (totally or partially) refractory to conventional treatment **Setting** Endometriosis Unit of Gynecology Division, Clinical Hospital, School of Medicine, University of Sao Paulo **Subgroup analysis** NA **Inclusion criteria** Age 18–45 years; diagnosis of deeply infiltrating endometriosis based on clinical history and demonstration of lesions on MRI or TVUS after bowel preparation; absence of clinical or laboratory signs of menopause or premature ovarian failure; presence of CPP refractory to ≥1 year conventional therapy; score 5 on 0-10 VAS. Must also have exhibited a set of signs and symptoms similar to adverse events caused by estrogen.63	**Group 1**: Potentized estrogen (12cH, 18cH, 24cH) *(ITT=19, PP=17)* **Group 2**: Placebo *(ITT=25, PP=24)*	**Potentized estrogen** prepared from 17-beta-estradiol valerate, lactose and hydro-alcoholic solution, administered in a dose of three drops twice daily (every 12 h). After initial assessment and delivery of the first vial (potency 12cH), subjects were evaluated by the investigator every 8 weeks. On visits 2 and 3, subjects were given new vials (visit 2: potency 18cH; visit 3: potency 24cH). **Placebo** identical vials containing hydroalcoholic solution only, indistinguishable in appearance and taste, with identical delivery	**Average variation in EAPP global score (VAS 0-50) from baseline to 24 weeks *(ITT analysis)*[64]** Group 1: MD 12.82; 95% CI 6.74, 18.89; p<0.001; due to significant reductions in VAS 0-10 partial scores (dysmenorrhoea, non-cyclic pelvic pain, cyclic bowel pain). Group 2*:* No significant change – but baseline scores were all notably lower than Group 1[65] **Average variation in QoL (SF-36) from baseline to 24 weeks *(PP analysis)*[66]** <u>Group 1:</u> Significant changes in bodily pain, vitality, and mental health, but not other domains <u>Group 2</u>*:* Non-significant changes in all domains – but baseline scores for many domains were notably different to Group 1 **Discontinuations** Group 1: 6/23 (26.1%) Group 2: 3/27 (11.1%)	Potentized estrogen (12cH, 18cH and 24cH) at a dose of 3 drops twice daily for 24 weeks was significantly more effective than placebo for reducing endometriosis-associated pelvic pain. As study limitations, sample size was small and duration of treatment and follow up was short. …the dropout rate (18%) points to the difficulty of keeping patients with severe disease and refractory to treatment in an RCT over a long period of time.	Adequate sequence generation: **Low risk** Allocation concealment: **Unclear** Blinding: **Low risk** Incomplete outcome data addressed: **High risk** Free of selective reporting: **High risk** Other bias: **Small study with imbalance between groups at baseline** <u>**Overall**</u>**: Very serious risk of bias**

Abbreviations: CI, confidence interval; CPP, chronic pelvic pain; EAPP, endometriosis-associated pelvic pain; F/U, follow-up; IHD, ischemic heart disease; IPD, inflammatory pelvic disease; ITT, intention to treat; IU, international units; PEA, palmitoylethanolamide; PP, per protocol; QoL, quality of life; MD, mean difference; MRI, magnetic resonance imaging; NA, not assessed; OCP, oral contraceptive pill; QoL, quality of life; SF-36, 36-item Short Form health survey; RCT, randomised clinical trial; RoB, risk of bias; TVUS, transvaginal ultrasound; VAS, visual analogue scale; VASQS, Visual Analogue Sleep Quality Scale.

[63] According to the paper, adverse events include anxiety, depression, insomnia, migraine and constipation, among others. "Individualisation of treatment according to similarity of signs and symptoms is a *sine qua non* requisite for the development of curative homeostatic response (clinical efficacy) and must mandatorily be included in all homeopathic clinical trials".

[64] Excluded 4 subjects in Group 1 and 2 subjects in Group 2 who withdrew consent.

[65] The publication reported that demographic and disease characteristics were broadly similar at baseline between the two groups but no statistical analyses were reported, except for depression symptoms (BDI score) which was significantly higher in Group 1 at baseline (p=0.004).

[66] Excluded subjects in each arm who discontinued, but included 4 subjects in Group 1 and 2 subjects in Group 2 who withdrew consent.

Adenomyosis

No relevant studies were identified.

Clinical evidence profile

Endometriosis

The EEWG subgroup for this research question agreed that all except two of the identified studies are at serious or very serious risk of bias and cannot be used as the basis for evidence-based recommendations. The two RCTs that were considered potentially worthy of further consideration by the EWG subgroup are:

- Schwertner et al 2013 (melatonin)
- Cobellis et al 2011 (micronised PEA/transpolydatin)

Table 52 Evidence Profile Table: Alternatives to pharmacological and surgical management – melatonin

No. of studies *References*	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients		Effect		Quality of evidence (GRADE)	Importance
						Melatonin	Placebo	Relative (95% CI)	Absolute		
Worst pain during the last 24 hours (daily) – reported on VAS											
1 RCT *Schwertner et al 2013*	No serious risk of bias	No serious inconsistency	Serious indirectness[1]	Serious imprecision[2]	None	20	20	39.30 [a] (12.88, 43.01)	AMD 1.80 lower (95% CI 0.59 lower to 1.97 lower) [b]	Low	CRITICAL
Pain during menstrual period (dysmenorrhoea) – reported on VAS											
1 RCT *Schwertner et al 2013*	No serious risk of bias	No serious inconsistency	Serious indirectness[1]	Serious imprecision[2]	None	20	20	38.1 [a] (15.96, 49.15)	AMD 2.6 lower (95% CI 0.38 lower to 1.71 lower) [b,c]	Low	CRITICAL
Pain during intercourse – reported on VAS											
1 RCT *Schwertner et al 2013*	No serious risk of bias	No serious inconsistency	Serious indirectness[1]	Serious imprecision[2]	None	20	20	23.02 [a] (6.90, 24.50)	AMD 1.40 lower (95% CI 0.42 lower to 1.49 lower) [b]	Low	CRITICAL
Pain during evacuation – reported on VAS											
1 RCT *Schwertner et al 2013*	No serious risk of bias	No serious inconsistency	Serious indirectness[1]	Serious imprecision[2]	None	20	20	34.60 [a] (19.84, 36.50)	AMD 2.18 lower (95% CI 1.25 lower to 2.30 lower) [b]	Low	CRITICAL

No. of studies *References*	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients		Effect		Quality of evidence (GRADE)	Importance
						Melatonin	Placebo	Relative (95% CI)	Absolute		
Pain during urination – reported on VAS											
1 RCT *Schwertner et al 2013*	No serious risk of bias	No serious inconsistency	Serious indirectness[1]	Serious imprecision[2]	None	20	20	27.65 [a] (6.47, 133.00)	AMD 1.13 lower (95% CI 0.41 lower to 1.75 lower) [b]	Low	CRITICAL

Abbreviations: AMD, adjusted mean difference; CI, confidence interval; RCT, randomised controlled trial; VAS, visual analogue scale.

a Relative change = adjusted mean difference/adjusted placebo mean x 100%

b Mixed analysis of variance model. Mean difference groups.

c There appears to be an error in the reported 95% CI as the point estimate does not fall within the interval.

1 The study used melatonin for an off-label indication at a dose that is five times the recommended dose for insomnia.

2 The confidence interval is large.

Table 53 Evidence Profile Table: Alternatives to pharmacological and surgical management – micronised PEA/transpolydatin

No. of studies *References*	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients			Effect	Quality of evidence (GRADE)	Importance
						Micronised PEA/ transpolydatin	Placebo/ Celecoxib	Relative (95% CI)	Absolute		
Change in median VAS pelvic pain – before laparoscopic surgery to 3 months											
1 RCT *Cobellis et al 2011*	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	None	21	20/ 20		Not calculable; favours celecoxib	Low	CRITICAL
Change in median VAS dysmenorrhoea – before laparoscopic surgery to 3 months											
1 RCT *Cobellis et al 2011*	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	None	21	20/ 20		Not calculable; favours celecoxib	Low	CRITICAL
Change in median VAS dyspareunia – before laparoscopic surgery to 3 months											
1 RCT *Cobellis et al 2011*	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	None	21	20/ 20		Not calculable; favours celecoxib	Low	CRITICAL

Abbreviations: RCT, randomised controlled trial; VAS, visual analogue scale.

1 Celecoxib group received a single course for 7 consecutive days whereas other arms received intervention for 3 months.

2 For some groups the range (shown graphically) was more than 2 on the VAS.

Adenomyosis

No relevant studies were identified.

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Clinical evidence statements

Comparison 1: Melatonin vs Placebo

Worst daily pain

Low quality evidence from 1 RCT (n=40) demonstrated a statistically significant beneficial effect of melatonin (10 mg tablets) compared with placebo in the reduction of worst pain in the last 24 hours (measured using VAS) at 8 weeks after starting treatment.

Dysmenorrhoea

Low quality evidence from 1 RCT (n=40) demonstrated a statistically significant beneficial effect of melatonin (10 mg tablets) compared with placebo in the reduction of dysmenorrhoea (measured using VAS) at 8 weeks after starting treatment.

Pain during intercourse

Low quality evidence from 1 RCT (n=40) demonstrated a statistically significant beneficial effect of melatonin (10 mg tablets) compared with placebo in the reduction of pain during intercourse (measured using VAS) at 8 weeks after starting treatment.

Pain during evacuation

Low quality evidence from 1 RCT (n=40) demonstrated a statistically significant beneficial effect of melatonin (10 mg tablets) compared with placebo in the reduction of pain during evacuation (measured using VAS) at 8 weeks after starting treatment.

Pain during urination

Low quality evidence from 1 RCT (n=40) demonstrated a statistically significant beneficial effect of melatonin (10 mg tablets) compared with placebo in the reduction of pain during urination (measured using VAS) at 8 weeks after starting treatment.

Comparison 2: Micronised PEA/transpolydatin vs placebo

Pelvic pain

Low quality evidence from 1 RCT (n=61) demonstrated a statistically significant beneficial effect of micronised PEA/transpolydatin (400 mg + 40 mg twice a day) compared with placebo in the reduction of pelvic pain (measured using VAS) at 3 months after starting treatment. However, the RCT demonstrated a statistically significant beneficial effect of celecoxib (200 mg twice a day for 7 consecutive days) compared with micronised PEA/transpolydatin or placebo.

Dysmenorrhoea

Low quality evidence from 1 RCT (n=61) demonstrated a statistically significant beneficial effect of micronised PEA/transpolydatin (400 mg + 40 mg twice a day) compared with placebo in the reduction of dysmenorrhoea (measured using VAS) at 3 months after starting treatment. However, the RCT demonstrated a statistically significant beneficial effect of celecoxib (200 mg twice a day for 7 consecutive days) compared with micronised PEA/transpolydatin or placebo.

Dyspareunia

Low quality evidence from 1 RCT (n=61) demonstrated a statistically significant beneficial effect of micronised PEA/transpolydatin (400 mg + 40 mg twice a day) compared with placebo in the reduction of dyspareunia (measured using VAS) at 3 months after starting treatment. However, the RCT demonstrated a statistically significant beneficial effect of celecoxib (200 mg twice a day for 7 consecutive days) compared with micronised PEA/transpolydatin or placebo.

Q9a – Surgical management

In people with endometriosis or adenomyosis, what is the effect of surgical treatment on patient outcomes?

Description of clinical evidence

The literature search date was **16 October 2019**.

Clinical evidence is summarised by comparator, as classified in the Research Protocol:

- surgery compared with diagnostic laparoscopy
- ablation compared with excision.

Surgery compared with diagnostic laparoscopy

22 potentially relevant SRs were identified. The identified SRs did not include any additional relevant RCTs that were missed from the literature search.

No additional studies comparing surgery with diagnostic laparoscopy were identified in the literature search.

Ablation versus excision

22 potentially relevant SRs were identified. The identified SRs did not include any additional relevant RCTs that were missed from the literature search.

One relevant RCT was identified, comparing ablation and excision surgery for superficial endometriosis-associated pain (Riley et al. 2019).

Summary of included studies

Surgery compared with diagnostic laparoscopy

No relevant studies were identified.

Ablation versus excision

Table 54 Evidence Summary: Laparoscopic excisional surgery versus ablative surgery– Endometriosis

Study details	Participants	Intervention *(n)*	Methods	Results	Authors conclusion	Cochrane RoB tool
Full citation Riley KA, Benton AS, Deimling TA, Kunselman AR, Harkins GJ. Surgical excision versus ablation for superficial endometriosis-associated pain: A randomized controlled trial. J Minimally Invasive Gynecology. 2019. 26:71-77. **Country** United States **Aim** To compare surgical excision and ablation of endometriosis for treatment of chronic pelvic pain. Hypothesis that improvement in symptoms would be found for excision. **F/U** 12 months **Source of funding** Pennsylvania State University, NIH/NCATS grant. One author has stock in Merck and another was a product tester for Covidien (now	**Population** Women with minimal to mild endometriosis undergoing laparoscopy **Setting** Single academic tertiary care hospital **Subgroup analysis** None **Inclusion criteria** Reproductive aged women with CPP or a known diagnosis of endometriosis who were planning to undergo laparoscopy. Included patients with an appearance of superficial endometriosis after an initial survey of the pelvis. Patients were not excluded if they had a previous laparoscopy to diagnose and treat endometriosis. **Exclusion criteria** Patients with DIE.	**Group 1** Ablation *(n=36 randomised, 21 at 6 months, 23 at 12 months)* **Group 2** Excision *(n=37 randomised, 22 at 6 months, 20 at 12 months)*	**Ablation** Using an argon beam coagulator through an assistant port. **Excision** Using the robotic monopolar diathermy scissor or spatula. All procedures were carried out using robotic-assisted laparoscopy to standardise the surgical approach for all patients. The surgical team included a single, high-volume minimally invasive gynaecologic surgeon with a focus on endometriosis, and a dedicated gynaecologic robotic and laparoscopic operating room team. Standardised perioperative care	**Mean change from baseline in non-menstrual pain at 6 months (VAS 1-100)** Ablation: -9.73 (95% CI -22.37, 2.90); p=0.13 Excision: -9.95 (95% CI -21.74, 1.83); p=0.10 Ablation vs excision: 0.22 (95% CI -17.06, 17.50); p=0.98 **Mean change from baseline in non-menstrual pain at 12 months (VAS 1-100)** Ablation: -10.41 (95% CI -25.00, 4.18); p=0.16 Excision: -9.46 (95% CI -24.05, 5.14); p=0.20 Ablation vs excision: -0.96 (95% CI -21.59, 19.68); p=0.93 **Mean change from baseline in dyspareunia at 6 months (VAS 1-100)** Ablation: -14.07 (95% CI -25.93, -2.21); **p=0.02** Excision: 8.89 (95% CI -2.00, 19.78); p=0.11 Ablation vs excision: -22.96 (95% CI -39.06, -6.86); **p=0.01** **Mean change from baseline in dyspareunia at 12 months (VAS 1-100)** Ablation: -9.40 (95% CI -23.19, 4.39); p=0.18 Excision: 2.66 (95% CI -10.31, 15.63); p=0.68 Ablation vs excision: -12.06 (95% CI -30.99, 6.87); p=0.21 **Mean change from baseline in dyschezia at 6 months (VAS 1-100)** Ablation: -4.45 (95% CI -15.87, 6.97); p=0.44 Excision: -1.73 (95% CI -12.51, 9.05); p=0.75 Ablation vs excision: -2.72 (95% CI -18.43, 12.99); p= 0.73	Treatment with ablation improved dysmenorrhoea at 6 and 12 months and improved dyspareunia at 6 months as compared with preoperative data. However, only dyspareunia demonstrated a significant difference between ablation and excision. Excision and ablation showed similar effectiveness for the treatment of pain associated with superficial endometriosis, with ablation showing more significant individual changes. Careful patient counseling regarding expectations of surgical intervention is vital in the management of endometriosis.	Adequate sequence generation: **Low risk** Allocation concealment: **Insufficient information** Blinding: **High risk (patients were blinded to treatment but clinicians not)** Incomplete outcome data addressed: **High risk** Free of selective reporting: **Low risk** Other bias: **Patients were allowed to continue their choice of standard medical suppression treatment for endometriosis** Robotic surgery for all procedures may limit generalisability. 52% of women (similar across arms) had LNG-IUD placed at the time of laparoscopy for concurrent management of endometriosis. **Overall: Serious risk of bias**

Study details	Participants	Intervention *(n)*	Methods	Results	Authors conclusion	Cochrane RoB tool
Medtronic Minimally Invasive Therapies)			through an ehanced recovery after surgery pathway. Randomisation was stratified by LNG-IUD placement at laparoscopy or non–LNG-IUD placement. No biopsy was performed.	**Mean change from baseline in dyschezia at 12 months (VAS 1-100)** Ablation: -7.70 (95% CI -21.52, 6.12); p=0.27 Excision: -2.53 (95% CI -16.31, 11.25); p=0.71 Ablation vs excision: -5.17 (95% CI -24.68, 14.35); p=0.60 **Mean change from baseline in dysmenorrhoea at 6 months (VAS 1-100)** Ablation: -26.99 (95% CI -41.48, -12.50); **p<0.001** Excision: -8.63 (95% CI -22.21, 4.95); p=0.21 Ablation vs excision: -18.36 (95% CI -38.22, 1.50); p=0.07 **Mean change from baseline in dysmenorrhoea at 12 months (VAS 1-100)** Ablation: -24.15 (95% CI -39.62, -8.68); **p=0.003** Excision: -14.80 (95% CI -30.48, 0.89); p=0.06 Ablation vs excision: -9.36 (95% CI -31.39, 12.68); p=0.40 **Mean change from baseline in QoL at 6 months (SF-12)** Ablation vs excision: Physical Component Summary: 1.93 (95% CI -3.74, 7.59); p=0.5 Mental Component Summary: 4.04 (95% CI -3.75, 11.84); p=0.3 **Mean change from baseline in QoL at 12 months (SF-12)** Ablation vs excision: Physical Component Summary: 6.85 (95% CI 0.16, 13.54); **p=0.04**[67] Mental Component Summary: 6.92 (95% CI -1.08, 14.92); p=0.09 **Drop-outs at 6 months** Ablation: 15/36 (42%) Excision: 15/37 (41%) **Drop-outs at 12 months** Ablation: 13/36 (36%) Excision: 17/37 (46%)		

[67] The authors have not commented on this statistically significant difference between groups, which is driven by the Role Physical and Bodily Pain domains. Baseline scores were not provided in the publication and there is no comment on whether scores were similar between groups at baseline.

Abbreviations: CI, confidence interval; CPP, chronic pelvic pain; DIE, deep infiltrating endometriosis; F/U, follow-up; SF-12, 12-item Short Form health survey; QoL, quality of life; VAS, visual analogue scale.

Clinical evidence profile

Surgery compared with diagnostic laparoscopy

No relevant studies were identified.

Ablation versus excision

Table 55 Evidence Profile Table: Laparoscopic excisional surgery versus ablative surgery – Endometriosis

No. of studies *References*	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients		Effect		Quality of evidence (GRADE)	Importance
						Ablation	Excision	Relative (95% CI)	Absolute (95% CI)		
Dyschezia at 6 months– reported on VAS (1-100 mm)											
1 RCT *Riley et al 2019*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	Serious[3]	None	21	22	NR	-2.72 (-18.43 to 12.99)	Very low	CRITICAL
Dyschezia at 12 months– reported on VAS (1-100 mm)											
1 RCT *Riley et al 2019*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	Serious[3]	None	23	20	NR	-5.17 (-24.68 to 14.35)	Very low	CRITICAL
Dyspareunia at 6 months– reported on VAS (1-100 mm)											
1 RCT *Riley et al 2019*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	Serious[3]	None	21	22	NR	**-22.96 (-39.06 to -6.86) Favours ablation**	Very low	CRITICAL
Dyspareunia at 12 months– reported on VAS (1-100 mm)											
1 RCT *Riley et al 2019*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	Serious[3]	None	23	20	NR	-12.06 (-30.99 to 6.87)	Very low	CRITICAL
Dysmenorrhoea at 6 months– reported on VAS (1-100 mm)											
1 RCT *Riley et al 2019*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	Serious[3]	None	21	22	NR	-18.36 (-38.22 to 1.50)	Very low	CRITICAL
Dysmenorrhoea at 12 months– reported on VAS (1-100 mm)											
1 RCT *Riley et al 2019*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	Serious[3]	None	23	20	NR	-9.36 (-31.39 to 12.68)	Very low	CRITICAL

No. of studies *References*	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients		Effect		Quality of evidence (GRADE)	Importance
						Ablation	Excision	Relative (95% CI)	Absolute (95% CI)		
Non-menstrual pelvic pain at 6 months– reported on VAS (1-100 mm)											
1 RCT *Riley et al 2019*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	Serious[3]	None	21	22	NR	0.22 (-17.06, 17.50)	Very low	CRITICAL
Non-menstrual pelvic pain at 12 months– reported on VAS (1-100 mm)											
1 RCT *Riley et al 2019*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	Serious[3]	None	23	20	NR	-0.96 (-21.59 to 19.68)	Very low	CRITICAL
QoL (mental component) at 6 months– reported on SF-12											
1 RCT *Riley et al 2019*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	No serious imprecision	None	21	22	NR	4.04 (-3.75 to 11.84)	Very low	IMPORTANT
QoL (mental component) 12 months– reported on SF-12											
1 RCT *Riley et al 2019*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	No serious imprecision	None	23	20	NR	6.92 (-1.08 to 14.92)	Very low	IMPORTANT
QoL (physical component) at 6 months– reported on SF-12											
1 RCT *Riley et al 2019*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	No serious imprecision	None	21	22	NR	1.93 (-3.74 to 7.59)	Very low	IMPORTANT
QoL (physical component) 12 months– reported on SF-12											
1 RCT *Riley et al 2019*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	No serious imprecision	None	23	20	NR	6.85 (0.16 to 13.54) Favours ablation	Very low	IMPORTANT

Abbreviations: CI, confidence interval; NR, not reported; RCT, randomised control trial; SF-12, 12-item Short Form health survey; QoL, quality of life; VAS, visual analogue scale.

1. No blinding of clinicians; patients were allowed to continue their choice of standard medical suppression treatment for endometriosis; between-group differences in baseline VAS and QoL scores are not reported.
2. Results may not be generalisable to non-robotic surgery, and may not be generalisable to moderate or severe endometriosis.
3. The confidence interval is large.

Clinical evidence statements

Excisional surgery versus ablative surgery for endometriosis

Pain scores (improvement from baseline in VAS scores at 6 and 12 months)

Very low-quality evidence from 1 RCT (n = 43 analysed) showed a *statistically significant* (but not clinically significant) beneficial effect of robotic laparoscopic ablation on dyspareunia at 6 months after surgery (measured using VAS) compared with robotic laparoscopic excision in people with minimal to mild superficial endometriosis. This difference was not statistically significant at 12 months after surgery. No significant differences between robotic surgical techniques were found in dyschezia, dysmenorrhoea or non-menstrual pelvic pain at 6 months and 12 months (all measured using VAS).

Quality of life (improvement from baseline in SF-12 scores at 6 and 12 months)

Very low-quality evidence from 1 RCT (n = 43 analysed) showed a *statistically significant* beneficial effect of robotic laparoscopic ablation on physical component summary score (measured using SF-12) compared with robotic laparoscopic excision in people with minimal to mild superficial endometriosis. This difference was not statistically significant at 6 months after surgery. No significant differences between robotic surgical techniques were found in the mental component summary score at 6 months or 12 months (measured using SF-12).

Q9b – Combination of surgery and hormonal treatment

In people with endometriosis or adenomyosis, do hormonal medical treatments before or after surgery improve patient outcomes?

Description of clinical evidence

A separate search was not performed for this question. Relevant literature was expected to be picked up in the searches for ablation and excision surgical management (Q9a; 16 October 2019) and hormonal medical treatments (Q7c; 15 October 2019).

The Research Protocol stipulates four relevant comparisons:

- hormonal medical treatment before surgery vs. placebo or no hormonal medical treatment before surgery
- hormonal medical treatment after surgery vs. placebo or no hormonal medical treatment after surgery
- hormonal medical treatment before surgery vs. hormonal medical treatment after surgery
- hormonal medical treatment before and after surgery vs. placebo or no hormonal medical treatment before and after surgery.

Endometriosis

One new relevant SR was identified:

- Levonorgestrel-releasing intrauterine system (LNG-IUS) as a postoperative maintenance therapy for endometriosis (Song et al 2018).

The identified SR did not include any additional relevant RCTs that were missed from the literature search.

Three new relevant RCTs were identified. These three trials are relevant to the comparison of hormonal medical treatment after surgery vs. placebo or no hormonal medical treatment after surgery.

Progestogen versus control

- LNG-IUS (with gonadotropin-releasing hormone [GnRH] agonist for 6 months) vs. expectant management alone (with GnRH agonist for 6 months) after laparoscopic ovarian cystectomy surgery (Chen et al 2017)

Progestogen versus placebo

- Desogestrel (for 24 weeks) vs. placebo after laparoscopic surgery (Tanmahasmut et al 2017)

GnRH agonist versus control

- GnRH agonist (for 12 months) vs. no treatment after laparoscopic surgery (Huang et al 2018)

A fourth RCT compared a progestogen (dienogest) with a GnRH agonist (leuprolide acetate) after surgery (Abdou et al 2018). This trial does not meet the eligibility criteria for this research question and has been included in the evidence base for hormonal medical treatments (Q7c).

Similar to the NICE Guideline, no studies were identified for inclusion for the following three comparisons:

- hormonal medical treatment before surgery vs. placebo or no hormonal medical treatment before surgery
- hormonal medical treatment before surgery vs. hormonal medical treatment after surgery
- hormonal medical treatment before and after surgery vs. placebo or no hormonal medical treatment before and after surgery.

Adenomyosis

No relevant trials were identified.

Summary of included studies

Endometriosis

Three new relevant RCTs were identified. One RCT compared a progestogen (LNG-IUS) plus a GnRH agonist with expectant management (including a GnRH agonist) (Chen et al 2017). The second compared an oral progestogen (desogestrel) with placebo (Tanmahasamut et al 2017). The third RCT compared a GnRH agonist (not specified) with control (Huang et al 2018).

Table 56 Evidence Summary: Hormonal medical treatments – Endometriosis – after surgery

Study details	Participants	Intervention *(n)*	Methods	Results	Authors conclusion	Cochrane RoB tool
Progestogen (+GnRH-a) vs. expectant management (+GnRH-a)						
Full citation Chen YJ, Hsu TF, Huang BS, Tsai HW, Chang YH, Wang PH. Postoperative maintenance levonorgestrel-releasing intrauterine system and endometrioma recurrence: a randomized controlled study. American Journal of Obstetrics & Gynecology. 2017. 216:582.e1-9. **Country** Northern Taiwan **Aim** To evaluate whether a maintenance levonorgestrel-releasing intrauterine system is effective for preventing postoperative endometrioma recurrence **F/U** 30 months **Source of funding** Ministry of Science and Technology, Taipei Veterans General Hospital, Yen-Tjing-Ling Medical Foundation, and the Szu-Yuan Research Foundation	**Population** Women with dysmenorrhoea and a sonographic diagnosis of endometrioma who were scheduled for elective laparoscopic ovarian cystectomy surgery **Setting** Tertiary medical centre **Subgroup analysis** None **Inclusion criteria** Moderate and severe symptomatic endometriosis (stages 3 and 4),[68] with a chocolate-containing cyst observed during laparoscopic surgery. **Exclusion criteria** The desire to become pregnant within 30 months; age <20 years or >43 years; inability to undergo conservative surgery; any hormonal therapy within the 3 months preceding surgery; a history of previous surgery for endometriosis; the use of GnRH-a; a clinical history of PID; uterine and adnexal pathologies other	**Group 1** LNG-IUS (Mirena) + GnRH-a *(number randomised=40)* **Group 2** Expectant management alone, including GnRH-a (control) *(number randomised=40)*	All subjects underwent laparoscopic ovarian cystectomy performed using mechanical instruments and electrosurgery. Adhesions were dissected and ovaries completely mobilised. Endometriomas were evacuated and excised using countertraction applied to pseudocapsule and normal ovarian tissue. Remaining fragments of ovarian endometrioma wall were fulgurated using electrocauterisation. After completion of laparoscopic cystectomy and before reversal of anesthesia, subjects were allocated to either group. For subjects in intervention group, an LNG-IUS was inserted into the uterine cavity under general anesthesia. Contraception method for the control group was condoms and periodic abstinence.	**Mean reduction in dysmenorrhoea from baseline to 30 months (VAS 0-100)** LNG-IUS *(n=40):* 60.8 ± SD 25.5 Control *(n=40):* 38.7 ± 25.9 p<0.001 Mean difference: 22.1 (95% CI 10.7, 33.5) **Mean reduction in non-cyclic pelvis pain from baseline to 30 months (VAS 0-100)** LNG-IUS *(n=27):* 39.1 ± 10.9 Control *(n=26):* 30.1 ± 14.7 p=0.014 Mean difference: 9.0 (95% CI 1.9, 16.1) **Endometrioma recurrence (<3cm) from baseline to 30 months** LNG-IUS: 10/40 (25%) Control: 15/40 (37.5%) P=0.228 RD: 12.5% (95% CI -7.6, 32.6) HR: 0.60 (95% CI 0.27, 1.33); p=0.209 **Endometrioma recurrence (<2cm) from baseline to 30 months** LNG-IUS: 13/40 (32.5%) Control: 17/40 (42.5%) HR: 0.68 (95% CI 0.33, 1.40); p=0.295 **Reoperation/further treatment after recurrence**	Long-term maintenance therapy using a LNG-IUS is not effective for preventing endometrioma recurrence. Although the follow-up period was described as 30 months in our study, maybe the true follow-up period is 24 months. Because all of the patients received GnRH-a for at least 6 month, no recurrence was detected during the first 6 months. GnRH-a was given to reduce LNG-IUS expulsion and to reduce surgical treatment failures (dropouts in the control group).	Adequate sequence generation: **Low risk** Allocation concealment: **Unclear (insufficient information)** Blinding: **High risk (double blinding not possible and most patients were aware)** Incomplete outcome data addressed: **High risk (differs per outcome, explanations not given)** Free of selective reporting: **Low risk** Other bias: **None** **Recurrent lesions were evaluated using ultrasonography rather than laparoscopy with histological confirmation; recurrence rate is also dependent on criteria**

[68] According to the revised American Society for Reproductive Medicine (ASRM) classification.

Study details	Participants	Intervention *(n)*	Methods	Results	Authors conclusion	Cochrane RoB tool
of Internal Medicine. The authors declared no COI.	than endometrioma (e.g. adenomyosis, leiomyoma, other ovarian pathologies); other contraindications for the use of LNG-IUS.		All subjects received postoperative GnRH-a injections every 4 weeks for 6 months. Specimens were submitted for histopathological evaluation to confirm presence of endometriosis in all patients. Endometrioma recurrence was defined via the ultrasound identification of a round mass with a thick wall, a minimum diameter of 3 cm, regular margins, and homogeneously low echogenic fluid content with scattered internal echoes, without papillary projection and with absent or poor vascularisation of capsule, and septa.	LNG-IUS: 1 (re-operation) Control: 8 (3 re-operations, 2 treated with contraceptive pills, 2 with gestrinone, 1 with LNG-IUS) **Discontinuation due to AE** No discontinuations due to AEs **Study discontinuation** LNG-IUS: 1 (removed at 15 months) Control: 0		**(size of endometrioma).** **Overall: Small sample size and very serious risk of bias.**
Progestogen vs. placebo						
Full citation Tanmahasamut P, Saejong R, Rattanachaiyanont M, Angsuwathana S, Techatraisak K, Sanga-Areekul N. Postoperative desogestrel for pelvic endometriosis-related pain: a randomized controlled trial. Gynecological Endocrinology. 2017. 33:534-539. **Country** Thailand **Aim** To determine the effectiveness of desogestrel for relieving endometriosis-related pain. **F/U** 6 months **Source of funding** Siriraj Research Development Fund. The authors declared no COI.	**Population** Patients with endometriosis and moderate-severe dysmenorrhoea and/or pelvic pain scheduled for laparoscopic surgery **Setting** Department of Obstetrics and Gynaecology, Faculty of Medicine Siriraj Hospital, Mahidol University **Subgroup analysis** None **Inclusion criteria** Women with moderate-to-severe dysmenorrhoea and/or pelvic pain for more than 6 months; scheduled for laparoscopic surgery. **Exclusion criteria** Uterine or adnexal anomalies other than endometriosis; current treatments for endometriosis other than analgesic medications;	**Group 1** Desogestrel *(number randomised=20)* **Group 2** Placebo *(number randomised=20)*	All subjects underwent laparoscopic surgery under general anesthesia. The operation was performed using only mechanical instruments and electrosurgery. Adhesions were dissected using microscissors. Ovaries were completely mobilised and endometriotic cysts were evacuated and excised by means of countertraction applied on its pseudocapsule and normal ovarian tissue using atraumatic forceps. The diagnosis of endometriosis was made by direct visualisation of typical endometriotic lesions. Histopathology of tissue samples confirming the	**Median change in overall pain from baseline to 6 months (VAS)** *Intention to treat* Desogestrel *(n=20)*: -84 (range: - 100, 19) Placebo *(n=20)*: -57 (-100, 0) p=0.005 *Per protocol* Desogestrel *(n=19)*: -85 (range:- 100, -50) Placebo *(n=19)*: -58 (-100, - 18) p=0.003 **Median change in dysmenorrhoea from baseline to 6 months (VAS)** *Intention to treat* Desogestrel *(n=20)*: -84 (range:- 100, 19) Placebo *(n=20)*: -61 (-96, 0) p=0.005 *Per protocol* Desogestrel *(n=19)*: -84 (range:- 100, -29)	Desogestrel is effective and acceptable for postoperative therapy for patients with moderate-to-severe pain related to endometriosis. As expected, both the placebo and desogestrel groups had improvement of pelvic pain and dysmenorrhoea at 6 months after surgery; but the magnitude of improvement was significantly greater in the desogestrel group. Studies with larger sample size and	Adequate sequence generation: **Low risk** Allocation concealment: **Low risk** Blinding: **Some concerns (double blinded but change in menstruation pattern might attenuate blinding efficacy)** Incomplete outcome data addressed: **High risk (differs by outcome)** Free of selective reporting: **Low risk** Other bias: **None** **Overall: Small sample size and serious risk of bias.**

Study details	Participants	Intervention *(n)*	Methods	Results	Authors conclusion	Cochrane RoB tool
	unable to undergo conservative surgery; contraindications to desogestrel; unable to tolerate menstrual changes; planned for pregnancy within 6 months; refused to participate in study.		diagnosis was available in 39 of 40 subjects. The trial medication was desogestrel 0.075 mg per tablet or placebo, taken once daily before bedtime for 24 weeks. The trial medications were put into the capsules that were identical in physical appearance to the placebo and were contained in identical package each of 28 capsules.	Placebo *(n=19)*: -61 (-96, -18) p=0.002 **Median change in noncyclic pelvic pain from baseline to 6 months (VAS)** *Intention to treat* Desogestrel *(n=18)*: -81 (range:- 100, 23) Placebo *(n=18)*: -51 (-100, 35) p=0.007 *Per protocol* Desogestrel *(n=17)*: -81 (range:- 100, -12) Placebo *(n=17)*: -52 (-100, 35) p=0.004 **Median change in dyspareunia from baseline to 6 months (VAS)** *Intention to treat* Desogestrel *(n=7)*: -59 (range:-91, 22) Placebo *(n=11)*: -51 (-84, 13) p=0.342 *Per protocol* Desogestrel *(n=6)*: -66 (-91, - 46) Placebo *(n=10)*: -52 (-64, 13) p=0.159 **Patient satisfaction (5-point Likert scale)**[69] Desogestrel Baseline: 82% very satisfied, 18% satisfied; 6 months: 100% satisfied Placebo Baseline: 95% very satisfied, 5% satisfied; 6 months: 47% very satisfied, 36% satisfied, 17% uncertain Desogestrel vs placebo Very satisfied RR: 23.2 (95% CI 2.6, 208.6); p=0.001 **Endometriosis recurrence from baseline to 6 months** One placebo patient had recurrent endometriotic cyst (by ultrasound) **Study discontinuation** Desogestrel: 1/20 (5%) lost to follow up	longer follow-up period are mandatory before the treatment is adopted in routine practice.	

[69] Percentages taken from graph.

Study details	Participants	Intervention *(n)*	Methods	Results	Authors conclusion	Cochrane RoB tool
				Placebo: 1/20 (5%) received depot medroxyprogesterone acetate		
GnRH-a vs. control						
Full citation. Huang C, Wu M, Liu Z, Shi H, Han Y, Song X. Clinical efficacy and safety of gonadotropin-releasing hormone agonist combined with laparoscopic surgery in the treatment of endometriosis. International Journal of Clinical and Experimental Medicine. 2018. 11:4132-4137. **Country** China **Aim** To investigate the clinical efficacy and safety of GnRH-a combined with laparoscopic surgery in the treatment of endometriosis. **F/U** 12 months **Source of funding** Not reported. Authors declared no COI.	**Population** Women with endometriosis **Setting** Department of Gynecology, Wuhan Children's Hospital **Subgroup analysis** None **Inclusion criteria** Endometriosis confirmed by histology; not planning to conceive immediately. **Exclusion criteria** Hormone therapy 3 months prior to surgery; endocrine, immune, metabolic diseases, or malignant tumors; laparoscopy or GnRH-a previously; contraindications against either laparoscopy or GnRH-a.	**Group 1** Laparoscopic surgery + GnRH-a *(n=50 randomised)* **Group 2** Control (laparoscopic surgery alone) *(n=50 randomised)*	All subjects underwent standard laparoscopic surgical procedures including release of pelvic adhesions, resection of ovarian endometriosis, and ectopic lesion resection/ electrocautery. Patients in the treatment group received additional GnRH-a treatment, which involved subcutaneous injection of GnRH-a with a dose of 3.75 mg on the first day after operation and continuously administered every 28 days, 4 to 6 times in total.	**Mean (SD) dysmenorrhoea at 12 months (NRS)** GnRH-a: 1.45±2.05 Control: 1.55±2.73 t=0.207; p=0.836[70] **Mean (SD) chronic pelvic pain at 12 months (NRS)** GnRH-a: 0.35±0.90 Control: 0.64±0.15 t=2.247; p=0.027[70] **Mean (SD) sexual intercourse pain at 12 months (NRS)** GnRH-a: 0.13±0.41 Control: 0.64±1.03 t=3.253; p=0.002[70] **Relief from dysmenorrhoea at 12 months (NRS)** GnRH-a: 11/13 (84.6%) Control: 4/11 (36.4%) X^2=5.919; p=0.015 **Relief from chronic pelvic pain at 12 months (NRS)** GnRH-a: 18/20 (90.0%) Control: 13/22 (63.6%) X^2=5.177; p=0.023 **Relief from sexual intercourse pain at 12 months (NRS)** GnRH-a: 4/7 (57.1%) Control: 1/2 (50.0%) X^2=0.032; p=1.000 **Endometriosis recurrence at 6 months[71]** GnRH-a: 6/50 (12.0%) Control: 15/50 (30.0%) X^2=4.882; p=0.027	Compared with laparoscopy use only, applying GnRH-a after laparoscopy can enhance treatment efficacy, increase pain relief rates, and reduce recurrence rates and partly adverse events. Our study also has some limitations. First, the sample size was limited, therefore, a larger sample size will be needed for further study and to fully evaluate the clinical efficacy and safety of this combination treatment. Second, the follow up duration was only one year. A longer follow up time will be necessary to further evaluate long-term clinical outcomes.	Adequate sequence generation: **Low risk** Allocation concealment: **Unclear (insufficient information)** Blinding: **High risk** Incomplete outcome data addressed: **High risk (different number of respondents per outcome, and flow chart and explanations not provided)** Free of selective reporting: **Low risk** Other bias: **None** *Details of which GnRH-a is used are not given.* *Analysed differences at endpoint rather than change from baseline. Dichotomous outcomes underpowered.* **Overall: Small sample size and very serious risk of bias.**

[70] Caution is required to interpret the results because pain before operation was *identical* between groups and *identical* for each type of pain (dysmenorrhoea, chronic pelvic pain, sexual intercourse pain).

[71] Recurrence was defined as "6 months after the operation, progressively aggravated pain recurred or pelvic mass was found in the vaginal ultrasound examination". It is not clear whether the reported rate is at 6 or 12 months.

Abbreviations: AE, adverse events; COI, conflict of interest; F/U, follow up; GnRH-a, gonadotrophin-releasing hormone agonist; HR, hazard ratio; LNG-IUS, levonorgestrel-releasing intrauterine system; MD, mean difference; NRS, numerical rating scale; PID, pelvic inflammatory disease; RoB, risk of bias; SD, standard deviation; VAS, visual analogue scale.

Adenomyosis

No relevant trials were identified.

Clinical evidence profile

Endometriosis

Comparison: Progestogen (levonorgestrel-releasing intrauterine system) + GnRH-a versus expectant management + GnRH-a

Table 57 Evidence Profile Table: Combination surgery plus hormonal treatment – Progestogen vs expectant management

No. of studies *References*	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients		Effect		Quality of evidence (GRADE)	Importance
						LNG-IUS	Control	Relative (95% CI)	Absolute (95% CI)		
Mean reduction in dysmenorrhoea from baseline to 30 months – reported on VAS (0-100 mm)											
1 RCT *Chen et al 2017*	Very serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	No serious imprecision	None	40	40	NR	MD: 22.1 (10.7 to 33.5) Favours LNG-IUS	Low	CRITICAL
Mean reduction in non-cyclic pelvis pain from baseline to 30 months– reported on VAS (0-100 mm)											
1 RCT *Chen et al 2017*	Very serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	No serious imprecision	None	27	26	NR	MD: 9.0 (1.9 to 16.1) Favours LNG-IUS	Low	CRITICAL
Discontinuation due to AE											
1 RCT *Chen et al 2017*	Very serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	NR	None	0/40 (0%)	0/40 (0%)	NR	NR No difference	Low	CRITICAL
Endometrioma recurrence rate (size<3cm) from baseline to 30 months											
1 RCT *Chen et al 2017*	Very serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	Serious imprecision[3]	None	10/40 (25.0%)	15/40 (37.5%)	HR: 0.60 (95% CI:0.27 to 1.33)	MD:12.5% (-7.6% to 32.6%) No difference	Very low	IMPORTANT
Endometrioma recurrence rate (size<2cm) from baseline to 30 months											
1 RCT *Chen et al 2017*	Very serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	Serious imprecision[3]	None	13/40 (32.5%)	17/40 (42.5%)	HR: 0.68 (0.33 to 1.40)	NR No difference	Very low	IMPORTANT

No. of studies *References*	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients		Effect		Quality of evidence (GRADE)	Importance
						LNG-IUS	Control	Relative (95% CI)	Absolute (95% CI)		
Reoperation/further treatment											
1 RCT *Chen et al 2017*	Very serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	NR	None	1/40 (2.5%)	8/40 (20%)	NR	NR	Low	IMPORTANT

Abbreviations: AE, adverse events; CI, confidence interval; GnRH-a, gonadotropin-releasing hormone agonist; HR: hazard ratio; LNG-IUS, levonorgestrel-releasing intrauterine system; MD, mean difference; NR, not reported; RCT, randomised control trial; VAS, visual analogue scale.

1.Not possible to blind investigators and most patients became aware of intervention group; different number of patients per outcome without explanations given; small sample size.

2. Study conducted in Northern Taiwan. All subjects received GnRH-a injections every 4 weeks for 6 months after surgery.

3. Large confidence interval.

Comparison: Progestogen (desogestrel) versus placebo

Table 58 Evidence Profile Table: Combination surgery plus hormonal treatment – Progestogen vs placebo

No. of studies *References*	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients		Effect		Quality of evidence (GRADE)	Importance
						Desogestrel	Placebo	Relative (95% CI)	Absolute		
Median change in overall pain from baseline to 6 months – reported on VAS (0-100 mm)											
1 RCT *Tanmahasmut et al 2017*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	Serious imprecision[3]	None	19	19	NR	27[4] Favours desogestrel	Very low	CRITICAL
Median change in dysmenorrhoea from baseline to 6 months – reported on VAS (0-100 mm)											
1 RCT *Tanmahasmut et al 2017*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	Serious imprecision[3]	None	19	19	NR	23[4] Favours desogestrel	Very low	CRITICAL
Median change in noncyclic pelvic pain from baseline to 6 months – reported on VAS (0-100 mm)											
1 RCT *Tanmahasmut et al 2017*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	Serious imprecision[3]	None	18	18	NR	30[4] Favours desogestrel	Very low	CRITICAL
Median change in dyspareunia from baseline to 6 months – reported on VAS (0-100 mm)											
1 RCT *Tanmahasmut et al 2017*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	Serious imprecision[3]	None	6	10	NR	14[4] No difference	Very low	CRITICAL

No. of studies *References*	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients		Effect		Quality of evidence (GRADE)	Importance
						Desogestrel	Placebo	Relative (95% CI)	Absolute		
Proportion of patients who rated the treatment as very satisfied at 6 months (5-point Likert scale)											
1 RCT *Tanmahasmut et al 2017*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	NR	None	100%[5]	47%[5]	RR 23.2 (95% CI 2.6 to 208.6)	NR Favours desogestrel	Very low	IMPORTANT
Endometriosis recurrence at 6 months											
1 RCT *Tanmahasmut et al 2017*	Serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	NR	None	0/19 0%	1/19 5.26%	NR	NR No difference	Very low	IMPORTANT

Abbreviations: AE, adverse events; CI, confidence interval; NR, not reported; RCT, randomised control trial; RR, risk ratio; VAS, visual analogue scale.

1. High dropout rates in some outcomes and differences were not explained; double blinding attempted but change in menstruation patterns essentially unblinded participants; small sample size.
2. Study conducted in Thailand.
3. Large range of results.
4. Calculated by evidence review team using summary data (median change in Desogestrel group minus median change in placebo group).
5. Results taken approximately from graph.

Comparison: GnRH-a versus control

Table 59 Evidence Profile Table: Combination surgery plus hormonal treatment – GNRH-a vs control

No. of studies *References*	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients		Effect		Quality of evidence (GRADE)	Importance
						GnRH-a	Placebo	Relative (95% CI)	Absolute		
Mean dysmenorrhoea at 12 months (NRS)											
1 RCT *Huang et al 2018*	Very serious risk of bias[1]	Serious inconsistency[2]	Serious indirectness[3]	No serious imprecision[4]	None	50	50	NR	-0.1[5] No difference	Very low	CRITICAL
Mean chronic pelvic pain at 12 months (NRS)											
1 RCT *Huang et al 2018*	Very serious risk of bias[1]	No serious inconsistency	Serious indirectness[3]	No serious imprecision[4]	None	50	50	NR	-0.29[5] Favours GnRH-a	Very low	CRITICAL
Mean sexual intercourse pain at 12 months (NRS)											
1 RCT *Huang et al 2018*	Very serious risk of bias[1]	Serious inconsistency[2]	Serious indirectness[3]	No serious imprecision[4]	None	50	50	NR	-0.51[5] Favours GnRH-a	Very low	CRITICAL

No. of studies *References*	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients		Effect		Quality of evidence (GRADE)	Importance
						GnRH-a	Placebo	Relative (95% CI)	Absolute		
Relief from dysmenorrhoea at 12 months (NRS)											
1 RCT *Huang et al 2018*	Very serious risk of bias[1]	Serious inconsistency[2]	Serious indirectness[3]	No serious imprecision[4]	None	11/13 (84.6%)	4/11 (36.4%)	NR	Favours GnRH-a	Very low	CRITICAL
Relief from chronic pelvic pain at 12 months (NRS)											
1 RCT *Huang et al 2018*	Very serious risk of bias[1]	No serious inconsistency	Serious indirectness[3]	No serious imprecision[4]	None	18/20 (90.0%)	13/22 (63.6%)	NR	Favours GnRH-a	Very low	CRITICAL
Relief from sexual intercourse pain at 12 months (NRS)											
1 RCT *Huang et al 2018*	Very serious risk of bias[1]	Serious inconsistency[2]	Serious indirectness[3]	No serious imprecision[4]	None	4/7 (57.1%)	1/2 (50.0%)	NR	No difference	Very low	CRITICAL
Endometriosis recurrence at 6 months[72]											
1 RCT Huang et al 2018	Very serious risk or bias	No serious inconsistency	Serious indirectness[3]	No serious imprecision[3]	None	6/50 (12.0%)	15/50 (30.0%)	NR	Favours GnRH-a	Very low	CRITICAL

Abbreviations: AE, adverse events; CI, confidence interval; GnRH-a, gonadotropin-releasing hormone agonist; HR: hazard ratio; LNG-IUS, levonorgestrel-releasing intrauterine system; MD, mean difference; NR, not reported; RCT, randomised control trial; VAS, visual analogue scale.

1.High risk of blinding bias; insufficient information on allocation concealment; large number of dropouts with no explanations and GnRH-a details not provided.

2. Inconsistencies when look at pain scores and pain relief rates within the study.

3. Study conducted in China.

4. Based on results from group means.

5. Calculated by evidence review team using summary data (mean in GnRH-a group minus mean in placebo group).

Adenomyosis

No relevant evidence was identified.

[72] Recurrence was defined as "6 months after the operation, progressively aggravated pain recurred or pelvic mass was found in the vaginal ultrasound examination". It is not clear whether the reported rate is at 6 or 12 months.

Clinical evidence statements

Endometriosis

Comparison: Progestogen (levonorgestrel-releasing intrauterine system) + GnRH agonist versus expectant management alone (+GnRH agonist) after laparoscopic surgery

Chen et al 2017 (Northern Taiwan) – Overall very serious risk of bias

Pain scores

Low quality evidence from 1 trial (n=80) found a statistically significant beneficial effect of postoperative LNG-IUS (plus a GnRH agonist for 6 months) compared with expectant management (including a GnRH agonist for 6 months) in the reduction of non-cyclic pelvic pain and dysmenorrhoea (measured using VAS) at 30 months after starting treatment.

Endometriosis recurrence

Very low quality evidence from 1 trial (n=80) found no significant difference between postoperative LNG-IUS (plus a GnRH agonist for 6 months) compared with expectant management (including a GnRH agonist for 6 months) in the reduction of endometrioma recurrence (size <2cm or <3cm) at 30 months after starting treatment.

Comparison: Progestogen (desogestrel) versus placebo after laparoscopic surgery

Tanmahasamut et al 2017 (Thailand) – Overall serious risk of bias

Overall pain, dysmenorrhoea and non-cyclic pelvic pain

Very low quality evidence from 1 trial (n=38) found a statistically significant beneficial effect of postoperative desogestrel (0.075 mg/day) compared with placebo in the reduction of overall pain, dysmenorrhoea and non-cyclic pelvic pain (measured using VAS) at 6 months after starting treatment.

Dyspareunia

Very low quality evidence from 1 trial (n=16) found no significant difference between postoperative desogestrel (0.075 mg/day) and placebo in the reduction of dyspareunia at 6 months after starting treatment.

Patient satisfaction

Very low quality evidence from 1 trial (n=38) found a significantly greater proportion of subjects who received postoperative desogestrel (0.075 mg/day) were very satisfied with their treatment compared with the placebo group (measured using a 5-point Likert scale) at 6 months after starting treatment.

Comparison: GnRH agonist versus control after laparoscopic surgery

Huang et al 2018 (China) – Overall very serious risk of bias

Pain scores

Very low quality evidence from 1 trial (n=100) found a statistically significant beneficial effect of postoperative GnRH agonist compared with no postoperative GnRH agonist (measured using NRS 0-10) in the reduction of chronic pelvic pain and sexual intercourse pain at 12 months after starting treatment. No significant difference was found between the groups in dysmenorrhoea.

Pain relief scores

Very low quality evidence from 1 trial (n=44) found a statistically significant beneficial effect of postoperative GnRH agonist compared with no postoperative GnRH agonist (measured using NRS 0-10) in rates of relief of chronic pelvic pain at 12 months after starting treatment.

Endometriosis recurrence

Very low quality evidence from 1 trial (n=100) found a statistically significant beneficial effect of postoperative GnRH agonist compared with no postoperative GnRH agonist in the reduction of endometriosis recurrence (defined as progressively aggravated pain recurrence or pelvic mass on ultrasound). It is unclear if the reported rates of recurrence refer to 6 months or 12 months after starting treatment.[73]

Adenomyosis

No relevant trials were identified.

Q9c – Hysterectomy

In people with endometriosis or adenomyosis, what is the effect of hysterectomy on patient outcomes?

Description of clinical evidence

The literature search date was **14 October 2019**.

Clinical evidence is summarised by comparator, as classified in the Research Protocol:

- hysterectomy versus no hysterectomy
- hysterectomy with oophorectomy versus hysterectomy without oophorectomy.

Hysterectomy versus no hysterectomy

4 potentially relevant SRs were identified. The identified SRs did not include any additional relevant primary studies that were missed from the literature search.

One relevant cohort study was identified, comparing health-related quality of life (HRQoL) in people with endometriosis before and after hysterectomy with bilateral salpingo-oophorectomy (Tan et al. 2013).

Hysterectomy with versus without oophorectomy

4 potentially relevant SRs were identified. The identified SRs did not include any additional relevant primary studies that were missed from the literature search.

No additional studies comparing hysterectomy with and without oophorectomy were identified in the literature search.

[73] Recurrence was defined as "6 months after the operation, progressively aggravated pain recurred or pelvic mass was found in the vaginal ultrasound examination".

Summary of included studies

Hysterectomy versus no hysterectomy

Table 60 Evidence Summary: Hysterectomy with oophorectomy for endometriosis

Study details	Participants	Intervention *(n)*	Methods	Results	Authors conclusion	CASP checklist for cohort studies
Full citation Tan BK, Maillou K, Mathur RS, Prentice A. A retrospective review of patient-reported outcomes on the impact on quality of life in patients undergoing total abdominal hysterectomy and bilateral salpingo-oophorectomy for endometriosis. Eur J Obstet Gynecol Reprod Biol 2013. 170:533-538. **Country** United Kingdom **Aim** To assess the impact on HRQoL in patients undergoing total abdominal hysterectomy and BSO for endometriosis. **F/U** 3 months **Source of funding** Not reported	**Population** Women undergoing total abdominal hysterectomy and BSO for endometriosis. N=16 (11 had ASRM stage 4, 1 had stage 3, 2 had stage 2, 2 had stage 1) **Setting** Retrospective review of women attending a reproductive medicine unit at a university hospital **Subgroup analysis** None **Inclusion criteria** Patients debilitated by symptoms due to endometriosis and in whom other treatments had failed; patients undergoing total abdominal hysterectomy and BSO. **Exclusion criteria** No exceptions reported.	**Intervention** Abdominal hysterectomy and BSO **Control** Prior to abdominal hysterectomy and BSO *(before-and-after study n=16)*	The EHP-30 questionnaire forms part of the service evaluation of women undergoing total abdominal hysterectomy and BSO for endometriosis at the unit. All women who were booked for the procedure were asked to complete the questionnaire preoperatively and 3 months following surgery. No details were provided about the surgical procedure, which "is performed only as a last report" for debilitating symptoms.	**HRQoL EHP-30 – median (range)**[74] Pain Before surgery: 70.45 (0.00–79.55) After surgery: 0.00 (0.00–38.64) n=16; P = 0.001 Control and powerlessness Before surgery: 87.50 (58.33–100.00) After surgery: 6.25 (0.00–50.00) n=16; P < 0.01 Emotional wellbeing Before surgery: 68.75 (12.50–95.83) After surgery: 14.58 (0.00–45.83) n=16; P < 0.01 Social support Before surgery: 71.88 (43.75–93.75) After surgery: 9.38 (0.00–62.50) n=16; P < 0.01 Self-image Before surgery: 75.00 (0.00–100.00) After surgery: 8.33 (0.00–66.67) n=16; P = 0.001 Work life Before surgery: 75.00 (20.00–100.00) After surgery: 0.00 (0.00–95.00) n=11; P = 0.003 Sexual intercourse Before surgery: 72.50 (45.00–100.00) After surgery: 22.50 (0.00–100.00) n=14; P = 0.001 Relationship with children Before surgery: 50.00 (0.00–75.00)	Total abdominal hysterectomy and BSO significantly improves HRQoL in patients debilitated by symptoms attributable to endometriosis and in whom other modalities of treatment have failed. A limitation of the study relates to the number of subjects studied and hence we would advise caution with regards to the findings. Further studies with larger number of study subjects are needed to reaffirm the results.	1. Did the study address a clearly focused issue? **Yes** 2. Was the cohort recruited in an acceptable way? **Low risk of bias** 3. Was the exposure measured accurately to minimise bias? **Unclear** 4. Were all the subjects classified into exposure groups using the same procedure? **Yes** Was the outcome measured accurately to minimise bias? **Yes** 6. Have authors identified all important confounding factors? **Unclear** 7. Have the authors taken account of confounding factors in the design and/or analyses? **Yes** 8. Was the follow up of subject complete enough? **Low risk for core domains, high risk for modular domains** 9. Was the follow up of subjects long enough? **Insufficient follow-up**

[74] P value given by Wilcoxon matched pairs test.

Study details	Participants	Intervention *(n)*	Methods	Results	Authors conclusion	CASP checklist for cohort studies
				After surgery: 0.00 (0.00–40.00) n=7; P = 0.027 <u>Medical profession</u> Before surgery: 28.13 (0.00–56.25) After surgery: 0.00 (0.00–62.50) n=10; P = 0.015 <u>Treatment</u> Before surgery: 83.33 (50.00–100.00) After surgery: 8.33 (0.00–50.00) n=9; P = 0.008 <u>Concern on infertility</u> Before surgery: 62.50 (0.00–87.50) After surgery: 21.88 (0.00–62.50) n=6; P = 0.068		10. What are the results of this study? **No selective reporting bias** 11. How precise are the results? **High risk of bias** 12. Do you believe the results? **No, low precision, small sample size** 13. Can the results be applied to the local population? **As a last line treatment only** 14. Do the results of this study fit with other available evidence? **Yes** 15. What are the implications of this study for practice? **None** Overall bias assessment**: High risk of bias**

Abbreviations: ASRM, American Society for Reproductive Medicine; BSO, bilateral salpingo-oophorectomy; EHP-30; Endometriosis Health Profile 30 questionnaire; HRQoL, health-related quality of life.

Hysterectomy with versus without oophorectomy

No new relevant studies were identified.

Clinical evidence profile

A clinical evidence profile is not shown because the identified evidence was one retrospective before-and-after study.

Clinical evidence statements

Hysterectomy versus no hysterectomy

Quality of life

Very low quality evidence from 1 retrospective before-and-after study (n=16) showed that health-related quality of life (HRQoL, measured using the Endometriosis Health Profile-30 [EHP-30]) at three months after hysterectomy with bilateral salpingo-oophorectomy was significantly improved in women with debilitating symptoms of endometriosis, compared with HRQoL before the operation.

Hysterectomy with versus without oophorectomy

No new evidence

Q10 – Management strategies to enhance fertility

In people with endometriosis with and without infertility, what is the effect of hormonal and surgical treatments on fertility?

Description of clinical evidence

A separate search was not performed for this question. Relevant literature was picked up in the searches for surgical management (Q9a; **16 October 2019**) and hormonal medical treatment (Q7c; **15 October 2019**).

A total of 84 studies were tagged from other questions as relevant to fertility in people with endometriosis. Of the 84 studies, 29 were from the search conducted for surgical management (ablation and excision), 22 were from the search for hormonal medical treatments, and 33 were from searches for other questions.

None of 84 studies met the eligibility criteria specified in the Research Protocol. The main reasons for study exclusion were that the population was undergoing other fertility treatments (e.g. in vitro fertilisation [IVF]), the study design was ineligible (e.g. cohort studies), and the publication date was earlier than the years specified in the Research Protocol (2016 or 2009 depending on population). Some randomised controlled trials were also excluded because the hormonal or surgical treatments examined were not specified in, or were explicitly excluded from, the Research Protocol (e.g. triptorelin).

Q11 – Follow-up

In people with endometriosis who are asymptomatic, do follow-up interventions improve primary patient outcomes?

Description of clinical evidence

A separate search was not performed for this question. Relevant literature was expected to be picked up in the searches for diagnosis of endometriosis (Q5a; 16 October 2019), ablation and excision surgery (Q9a; 16 October 2019), hysterectomy (Q9c; 14 October 2019), and hormonal medical therapy (Q7c; 15 October 2019).

No relevant studies relating to the 'follow-up' interventions specified in the Research Protocol were identified.

Q12 – Secondary prevention

In people who have received treatment for endometriosis, what interventions prevent the recurrence of endometriosis symptoms and lesions?

Description of clinical evidence

Secondary prevention of the recurrence of endometriosis and endometriosis-associated pain is clinically important in view of the recurrence rates reported after endometriosis surgery. The primary focus for secondary prevention of endometriosis is typically on postoperative hormonal therapies. The ESHRE 2013 Guideline notes that postoperative adjunctive hormonal therapies for endometriosis can be prescribed in two situations: (i) for secondary prevention, which is defined as prevention of the recurrence of pain symptoms or the recurrence of disease in the long-term (more than 6 months after surgery); and (ii) short-term treatment (within 6 months after surgery) with the aim of improving the outcome of surgery for pain.

Although the NICE 2017 Guideline did not explicitly distinguish these two situations when considering evidence relating to the effectiveness of hormonal treatment before or after surgery for treatment of endometriosis, they did assess longer term recurrence of endometriosis and reoperation rates. Therefore, the question on combination surgery and hormonal treatment (Q9b) already addresses secondary prevention of endometriosis using hormonal medical treatments. 'Recurrence' is also an outcome in other research questions relating to management: Q7b (neuromodulators), Q7c (hormonal medical treatments), Q8 (alternatives to pharmacological and surgical management), Q9a (surgical management) and Q9c (hysterectomy). Furthermore, recurrence is an outcome for Q11, which addresses follow up (including prophylactic surgery) in people who have received treatment and are asymptomatic.

As such, a separate search was not performed for this question. It was anticipated that evidence relevant to secondary prevention of endometriosis would 'fall out' from other questions.

Prophylactic surgery

No relevant RCTs were identified.

Hormonal medical treatment after surgery

Two new relevant RCTs were identified. These two trials were included in Q9b and are relevant to the comparison of hormonal medical treatment after surgery vs. placebo or no hormonal medical treatment after surgery.

Progestogen versus control

- LNG-IUS (with gonadotropin-releasing hormone [GnRH] agonist for 6 months) vs. expectant management alone (with GnRH agonist for 6 months) after laparoscopic ovarian cystectomy surgery (Chen et al 2017)

GnRH agonist versus control

- GnRH agonist (for 12 months) vs. no treatment after laparoscopic surgery (Huang et al 2018)

Long-term hormonal medical treatments

No relevant RCTs were identified.

Summary of included studies

Table 61 Evidence Summary: Secondary prevention

Study details	Participants	Intervention *(n)*	Methods	Results	Authors conclusion	Cochrane RoB tool
Progestogen (+GnRH-a) vs. expectant management (+GnRH-a)						
Full citation Chen YJ, Hsu TF, Huang BS, Tsai HW, Chang YH, Wang PH. Postoperative maintenance levonorgestrel-releasing intrauterine system and endometrioma recurrence: a randomized controlled study. American Journal of Obstetrics & Gynecology. 2017. 216:582.e1-9. **Country** Northern Taiwan **Aim** To evaluate whether a maintenance levonorgestrel-releasing intrauterine system is effective for preventing postoperative endometrioma recurrence **F/U** 30 months **Source of funding** Ministry of Science and Technology, Taipei Veterans General Hospital, Yen-Tjing-Ling Medical Foundation, and the Szu-Yuan Research Foundation of Internal Medicine. The authors declared no COI.	**Population** Women with dysmenorrhoea and a sonographic diagnosis of endometrioma who were scheduled for elective laparoscopic ovarian cystectomy surgery **Setting** Tertiary medical centre **Subgroup analysis** None **Inclusion criteria** Moderate and severe symptomatic endometriosis (stages 3 and 4),[75] with a chocolate-containing cyst observed during laparoscopic surgery. **Exclusion criteria** The desire to become pregnant within 30 months; age <20 years or >43 years; inability to undergo conservative surgery; any hormonal therapy within the 3 months preceding surgery; a history of previous surgery for endometriosis; the use of GnRH-a; a clinical history of PID; uterine and adnexal pathologies other than endometrioma (e.g. adenomyosis, leiomyoma, other ovarian pathologies); other contraindications for the use of LNG-IUS.	**Group 1** LNG-IUS (Mirena) + GnRH-a *(number randomised=40)* **Group 2** Expectant management alone, including GnRH-a (control) *(number randomised=40)*	All subjects underwent laparoscopic ovarian cystectomy performed using mechanical instruments and electrosurgery.[76] After completion of laparoscopic cystectomy and before reversal of anesthesia, subjects were allocated to either group. For subjects in intervention group, an LNG-IUS was inserted into the uterine cavity under general anesthesia. Contraception method for the control group was condoms and periodic abstinence. All subjects received postoperative GnRH-a injections every 4 weeks for 6 months. Specimens were submitted for histopathological evaluation to confirm presence of endometriosis in all patients. Endometrioma recurrence was defined via the ultrasound identification of a round mass with a thick wall, a minimum diameter of 3 cm, regular margins, and homogeneously low echogenic fluid content with scattered internal echoes, without papillary	**Endometrioma recurrence (<3cm) from baseline to 30 months** LNG-IUS: 10/40 (25%) Control: 15/40 (37.5%) P=0.228 RD: 12.5% (95% CI -7.6, 32.6) HR: 0.60 (95% CI 0.27, 1.33); p=0.209 **Endometrioma recurrence (<2cm) from baseline to 30 months** LNG-IUS: 13/40 (32.5%) Control: 17/40 (42.5%) HR: 0.68 (95% CI 0.33, 1.40); p=0.295 **Dysmenorrhoea recurrence from baseline to 30 months** LNG-IUS: 6/40 (15.0%) Control: 15/40 (37.5%) HR: 0.32 (95% CI 0.12, 0.83); p=0.019 **Reoperation/further treatment after recurrence** LNG-IUS: 1 (re-operation) Control: 8 (3 re-operations, 2 treated with contraceptive pills, 2 with gestrinone, 1 with LNG-IUS) **Discontinuation due to AE** No discontinuations due to AEs **Study discontinuation** LNG-IUS: 1 (removed at 15 months) Control: 0	Long-term maintenance therapy using a LNG-IUS is not effective for preventing endometrioma recurrence. Although the follow-up period was described as 30 months in our study, maybe the true follow-up period is 24 months. Because all of the patients received GnRH-a for at least 6 month, no recurrence was detected during the first 6 months. GnRH-a was given to reduce LNG-IUS expulsion and to reduce surgical treatment failures (dropouts in the control group).	Adequate sequence generation: **Low risk** Allocation concealment: **Unclear (insufficient information)** Blinding: **High risk (double blinding not possible and most patients were aware)** Incomplete outcome data addressed: **High risk (differs per outcome, explanations not given)** Free of selective reporting: **Low risk** Other bias: **None** **Recurrent lesions were evaluated using ultrasonography rather than laparoscopy with histological confirmation; recurrence rate is also dependent on criteria (size of endometrioma).** **Overall: Small sample size and very serious risk of bias.**

[75] According to the revised American Society for Reproductive Medicine (ASRM) classification.

[76] Adhesions were dissected and ovaries completely mobilised. Endometriomas were evacuated and excised using countertraction applied to pseudocapsule and normal ovarian tissue. Remaining fragments of ovarian endometrioma wall were fulgurated using electrocauterisation.

Study details	Participants	Intervention *(n)*	Methods	Results	Authors conclusion	Cochrane RoB tool
			projection and with absent or poor vascularisation of capsule, and septa. Dysmenorrhoea recurrence was defined as a pain score greater than 50 mm on 0-100 mm VAS after 3 months of postoperative pain relief.			
GnRH-a vs. control						
Full citation. Huang C, Wu M, Liu Z, Shi H, Han Y, Song X. Clinical efficacy and safety of gonadotropin-releasing hormone agonist combined with laparoscopic surgery in the treatment of endometriosis. International Journal of Clinical and Experimental Medicine. 2018. 11:4132-4137. **Country** China **Aim** To investigate the clinical efficacy and safety of GnRH-a combined with laparoscopic surgery in the treatment of endometriosis. **F/U** 12 months **Source of funding** Not reported. Authors declared no COI.	**Population** Women with endometriosis **Setting** Department of Gynecology, Wuhan Children's Hospital **Subgroup analysis** None **Inclusion criteria** Endometriosis confirmed by histology; not planning to conceive immediately. **Exclusion criteria** Hormone therapy 3 months prior to surgery; endocrine, immune, metabolic diseases, or malignant tumors; laparoscopy or GnRH-a previously; contraindications against either laparoscopy or GnRH-a.	**Group 1** Laparoscopic surgery + GnRH-a *(n=50 randomised)* **Group 2** Control (laparoscopic surgery alone) *(n=50 randomised)*	All subjects underwent standard laparoscopic surgical procedures including release of pelvic adhesions, resection of ovarian endometriosis, and ectopic lesion resection/ electrocautery. Patients in the treatment group received additional GnRH-a treatment, which involved subcutaneous injection of GnRH-a with a dose of 3.75 mg on the first day after operation and continuously administered every 28 days, 4 to 6 times in total. Recurrence was defined as "6 months after the operation, progressively aggravated pain recurred or pelvic mass was found in the vaginal ultrasound examination". It is not clear whether the reported rate is at 6 or 12 months.	**Endometriosis recurrence at 6 months** GnRH-a: 6/50 (12.0%) Control: 15/50 (30.0%) X^2=4.882; p=0.027 **Study discontinuation** Not stated in publication although it is implied that no patients discontinued	Compared with laparoscopy use only, applying GnRH-a after laparoscopy can enhance treatment efficacy, increase pain relief rates, and reduce recurrence rates and partly adverse events. Our study also has some limitations. First, the sample size was limited, therefore, a larger sample size will be needed for further study and to fully evaluate the clinical efficacy and safety of this combination treatment. Second, the follow up duration was only one year. A longer follow up time will be necessary to further evaluate long-term clinical outcomes.	Adequate sequence generation: **Low risk** Allocation concealment: **Unclear (insufficient information)** Blinding: **High risk** Incomplete outcome data addressed: **High risk (different number of respondents per outcome, and flow chart and explanations not provided)** Free of selective reporting: **Low risk** Other bias: **None** *Details of which GnRH-a is used are not given.* *Analysed differences at endpoint rather than change from baseline. Dichotomous outcomes underpowered.* **<u>Overall</u>: Small sample size and very serious risk of bias.**

Abbreviations: AE, adverse events; CI, confidence interval; GnRH-a, gonadotropin-releasing hormone agonist; HR: hazard ratio; LNG-IUS, levonorgestrel-releasing intrauterine system; NR, not reported; RCT, randomised control trial; VAS, visual analogue scale.

Clinical evidence profile

Comparison: Progestogen (levonorgestrel-releasing intrauterine system) + GnRH-a versus expectant management + GnRH-a

Table 62 Evidence Profile Table: Secondary prevention – Progestogen vs expectant management

No. of studies *References*	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients		Effect		Quality of evidence (GRADE)	Importance
						LNG-IUS	Control	Relative (95% CI)	Absolute (95% CI)		
Endometrioma recurrence (size<3cm on ultrasound) from baseline to 30 months											
1 RCT *Chen et al 2017*	Very serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	Serious imprecision[3]	None	10/40 (25.0%)	15/40 (37.5%)	HR: 0.60 (95% CI:0.27 to 1.33)	RD:12.5% (-7.6% to 32.6%) No difference	Very low	CRITICAL
Endometrioma recurrence (size<2cm on ultrasound) from baseline to 30 months											
1 RCT *Chen et al 2017*	Very serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	Serious imprecision[3]	None	13/40 (32.5%)	17/40 (42.5%)	HR: 0.68 (0.33 to 1.40)	NR No difference	Very low	CRITICAL
Dysmenorrhoea recurrence (pain score greater than 50 mm on 0-100 mm VAS) from baseline to 30 months											
1 RCT *Chen et al 2017*	Very serious risk of bias[1]	No serious inconsistency	Serious indirectness[2]	Serious imprecision[3]	None	6/40 (15.0%)	15/40 (37.5%)	HR: 0.32 (0.12 to 0.83)	NR Favours LNG-IUS	Very low	CRITICAL

Abbreviations: AE, adverse events; CI, confidence interval; GnRH-a, gonadotropin-releasing hormone agonist; HR: hazard ratio; LNG-IUS, levonorgestrel-releasing intrauterine system; NR, not reported; RCT, randomised control trial; RD, risk difference; VAS, visual analogue scale.

1.Not possible to blind investigators and most patients became aware of intervention group; different number of patients per outcome without explanations given; small sample size.

2. Study conducted in Northern Taiwan. All subjects received GnRH-a injections every 4 weeks for 6 months after surgery.

3. Large confidence interval.

Comparison: GnRH-a versus control

Table 63 Evidence Profile Table: Secondary prevention – GNRH-a vs control

No. of studies *References*	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients		Effect		Quality of evidence (GRADE)	Importance
						GnRH-a	Placebo	Relative (95% CI)	Absolute		
Endometriosis recurrence at 6 months[77]											
1 RCT Huang et al 2018	Very serious risk or bias	No serious inconsistency	Serious indirectness[3]	No serious imprecision[3]	None	6/50 (12.0%)	15/50 (30.0%)	NR	Favours GnRH-a	Very low	CRITICAL

Abbreviations: AE, adverse events; CI, confidence interval; GnRH-a, gonadotropin-releasing hormone agonist; HR: hazard ratio; LNG-IUS, levonorgestrel-releasing intrauterine system; MD, mean difference; NR, not reported; RCT, randomised control trial; VAS, visual analogue scale.

1.High risk of blinding bias; insufficient information on allocation concealment; large number of dropouts with no explanations and GnRH-a details not provided.

2. Inconsistencies when look at pain scores and pain relief rates within the study.

3. Study conducted in China.

4. Based on results from group means.

5. Calculated by evidence review team using summary data (mean in GnRH-a group minus mean in placebo group).

[77] Recurrence was defined as "6 months after the operation, progressively aggravated pain recurred or pelvic mass was found in the vaginal ultrasound examination". It is not clear whether the reported rate is at 6 or 12 months.

Clinical evidence statements

Comparison: Progestogen (levonorgestrel-releasing intrauterine system) + GnRH agonist versus expectant management alone (+GnRH agonist) after laparoscopic surgery

Chen et al 2017 (Northern Taiwan) – Overall very serious risk of bias

Very low quality evidence from 1 trial (n=80) found no significant difference between postoperative LNG-IUS (plus a GnRH agonist for 6 months) compared with expectant management (including a GnRH agonist for 6 months) in the reduction of endometrioma recurrence (size <2cm or <3cm) at 30 months after starting treatment.

Very low quality evidence from 1 trial (n=80) found a statistically significant beneficial effect of postoperative LNG-IUS (plus a GnRH agonist for 6 months) compared with expectant management (including a GnRH agonist for 6 months) on recurrence of dysmenorrhoea (defined as a pain score greater than 50 mm on 0-100 mm VAS) at 30 months after starting treatment.

Comparison: GnRH agonist versus control after laparoscopic surgery

Huang et al 2018 (China) – Overall very serious risk of bias

Very low quality evidence from 1 trial (n=100) found a statistically significant beneficial effect of postoperative GnRH agonist compared with no postoperative GnRH agonist in the reduction of endometriosis recurrence (defined as progressively aggravated pain recurrence or pelvic mass on ultrasound). It is unclear if the reported rates of recurrence refer to 6 months or 12 months after starting treatment.[78]

[78] Recurrence was defined as "6 months after the operation, progressively aggravated pain recurred or pelvic mass was found in the vaginal ultrasound examination".

Evidence to decision deliberations

Appendix D provides a list of citations for all included studies identified in the literature search update, by research question. The EEWG subgroups were provided with full publications of the new studies prior to Evidence-to-Decision deliberations.

Q1 – Signs and symptoms

Table 64 EtD considerations for Q1 – Signs and symptoms

Assessment	EEWG judgement	EEWG considerations
Problem Is the problem a priority?	Yes	The EEWG agreed with the NICE guideline development Committee that one of the keys to earlier diagnosis, avoiding unnecessary pain, distress and possible disease progression, is awareness and knowledge of endometriosis among health professionals. People with endometriosis often find health professionals normalise their symptoms and have limited knowledge of endometriosis, which can contribute to a delay in diagnosis and increase the risk of misdiagnosis.
Desirable effects How substantial are the desirable anticipated effects?	Large	The EEWG agreed with the NICE Committee that GPs do not always suspect endometriosis and that earlier diagnostic investigation of symptoms would be of benefit to people with endometriosis. They agreed that confirmation of a diagnosis generally improves quality of life and emotional wellbeing of people who have had long-term symptoms in terms of recognition and explanation of their symptoms, and because it provides a gateway for accessing further information and support. They agreed that no confirmation of a diagnosis following investigation can be difficult for people who have had symptoms.
Undesirable effects How substantial are the undesirable anticipated effects?	Moderate	The EEWG discussed that an undesirable effect could be over-diagnosis. The EEWG agreed with the NICE Committee about the need to distinguish pain symptoms that are associated specifically with endometriosis, and to distinguish physiological from pathological pain associated with endometriosis in order to help GPs decide which people required further investigation.
Certainty of evidence What is the overall certainty of the evidence of effects?	No new included studies	No new evidence met the eligibility criteria. The EEWG noted that comparative cohort studies assessing signs and symptoms of endometriosis were identified in the literature search update but these studies were excluded due to the population being confirmed endometriosis; the study not performing multivariate analysis and/or not adjusting for confounders. The EEWG noted that the NICE guidance was informed by three studies that were all assessed as having moderate risk of bias according to the NICE prognostic study checklist. The EEWG agreed with the NICE Committee that mild dysmenorrhoea was not significantly associated with a diagnosis of endometriosis but that more severe dysmenorrhoea would be associated with endometriosis and that dysmenorrhoea, pelvic pain and a history of infertility would be significantly associated with more severe endometriosis. The EEWG noted that fatigue did not come up in the evidence base but is commonly reported by people with endometriosis and this may be an area for further research.
Values Is there important uncertainty about or variability in how much people value the main outcomes?	No important uncertainty or variability	The EEWG acknowledged that systematic study of patients' values and preferences was not undertaken. However, the EEWG agreed that people would value confirmation of a diagnosis and that no confirmation of a diagnosis following investigation can be difficult for people who have had symptoms.
Balance of effects Does the balance between desirable and undesirable effects favour the intervention or the comparison?	Don't know	
Acceptability Is the intervention acceptable to key stakeholders?	Don't know	
Feasibility Is the intervention feasible to implement?	Probably yes	

Assessment	EEWG judgement	EEWG considerations
Type of guidance developed by EEWG	Evidence-based Recommendation and Consensus Recommendations	**ADOPTED** Evidence-based Recommendation **#5** in the Full NICE Guideline. The EEWG changed terminology from chronic pelvic pain to persistent pelvic pain. **ADOPTED** Consensus Recommendations **#6**, **#7** and **#8** in the Full NICE Guideline. *Refer to Table App 3 for the wording of NICE recommendations.*

Q2a – Information and support

Table 65 EtD considerations for Q2a – Information and support

Assessment	EEWG judgement	EEWG considerations
Problem Is the problem a priority?	Yes	The EEWG agreed with the NICE guideline development Committee that the delay in a diagnosis means that many people with endometriosis have been told their symptoms are normal, which can lead to isolation, stress, depression and exhaustion through coping with symptoms without information and support. The EEWG agreed with the NICE Committee that accurate, evidence-based, up-to-date and easily accessible information is crucial to support people to understand and self-manage the condition.
Desirable effects How substantial are the desirable anticipated effects?	Varies	The EEWG agreed that the impact of information and support will depend on whether the person has a diagnosis or not. The impact will be moderate for people with a diagnosis (who can presumably access information from their healthcare provider) and large for people without a diagnosis.
Undesirable effects How substantial are the undesirable anticipated effects?	Small	The provision of accurate, evidence-based, up-to-date and easily accessible information is unlikely to create undesirable effects.
Certainty of evidence What is the overall certainty of the evidence of effects?	No new included studies	The EEWG noted that the literature search update for the Australian Guideline did not identify any new evidence on information and support. The EEWG discussed that comparative studies of the impact of information and support on the quality of life, wellbeing and decision-making of people with suspected or confirmed endometriosis are most informative for assessing effectiveness, but qualitative studies are useful for exploring areas of information and support that people find helpful, and for identifying how people would like to receive information and support. The EEWG considered the deliberations by the NICE Committee on the qualitative evidence identified. The EEWG noted that the included studies were judged to be of moderate to low quality and there were notable limitations in the evidence base. However, there were several important themes that emerged: frustrations related to a delay in diagnosis, social support and the psychological impact of endometriosis. Themes relating to the perspective and involvement of partners of people with endometriosis were also considered important by the NICE Committee in drafting the recommendations. The EEWG noted that the NICE Committee developed recommendations based on the themes identified in their literature review.
Values Is there important uncertainty about or variability in how much people value the main outcomes?	Possibly important uncertainty or variability	The EEWG discussed variability in how much people with suspected or confirmed endometriosis value information and support, and their differing needs. For example, the needs of menopausal people would be different to adolescents, and people with fertility issues have different concerns to those with pain. The EEWG acknowledged that systematic study of patients' values and preferences was not undertaken and so uncertainty exists about the patient's perspective.
Balance of effects Does the balance between desirable and undesirable effects favour the intervention or the comparison?	Favours the intervention	The EEWG noted that the evidence included in the NICE review showed that people with endometriosis found information and support provided through all forms (e.g. support groups, written or online, face to face) to be helpful, and this information enabled them to be actively involved in decision-making for the management and treatment of endometriosis. The EEWG noted that the evidence also identified barriers that people and their support network faced in their endometriosis pathway.
Acceptability Is the intervention acceptable to key stakeholders?	Yes	The EEWG agreed with the NICE Committee that it is important that the person understands the consequences of their choices and is able to make an informed decision. The challenge for healthcare professionals is to tailor information to the individual needs, preferences and circumstances of each person while also allowing for flexibility because information needs may also change with time or if new symptoms develop.

Assessment	EEWG judgement	EEWG considerations
Feasibility Is the intervention feasible to implement?	Yes	The EEWG noted that information and support is not a costly intervention, and that many support groups are patient-led or volunteer-led. The EEWG noted that the NICE Committee deliberately chose not to undertake an economic evaluation for the question on information and support as this topic was thought to be clinically uncontroversial.
Type of guidance developed by EEWG	Evidence-based Recommendations and Consensus Recommendations and Committee Opinion	**ADAPTED** Evidence-based Recommendation **#13** in the Full NICE Guideline. The EEWG changed the word 'psychological' to 'psychosocial'. The EEWG discussed that this recommendation does not provide clear implementation direction but is validating for people with endometriosis. **ADAPTED** Evidence-based Recommendation **#14** in the Full NICE Guideline. The EEWG added co-existing conditions to the list of factors to consider. **ADAPTED** Consensus Recommendation **#15** in the Full NICE Guideline. The EEWG clarified that information and support should be 'comprehensive and ongoing'. The EEWG also added that information on treatment options should include care, follow-up, anticipated waiting times and out of pocket expenses. **ADAPTED** Consensus Recommendation **#16** in the Full NICE Guideline. The EEWG removed reference to the NICE Guideline on patient experience in the NHS as this is not relevant to the Australian context. *Refer to Table App 2 for the wording of NICE recommendations.* **NEW** Committee Opinion on equitable access to care for people in rural and remote areas.

Q2b – Risk of cancer

Table 66 EtD considerations for Q2b – Risk of cancer

Assessment	EEWG judgement	EEWG considerations
Problem Is the problem a priority?	Yes	The EEWG noted that many people with endometriosis ask questions about whether or not the condition is associated with an increased risk of cancer. However, it was agreed that a systematic review of this topic would not be undertaken for the Australian Guideline as it is expected to consume considerable resources but not identify any new high quality evidence.
Certainty of evidence What is the overall certainty of the evidence of effects?	No systematic review update was performed	The EEWG noted that very large population-based studies were identified in the systematic review for the NICE Guideline but the NICE guideline development Committee were cautious about drawing conclusions from the results because the evidence base was generally of low to very low quality and an absolute risk could not be derived from the data. *Refer to Table App 11 for NICE evidence statements.* The EEWG opted to make a statement about the lack of high quality definitive evidence available and referred to information on the risk of endometrial cancer and endometriosis published by Cancer Australia.
Balance of effects Does the balance between desirable and undesirable effects favour the intervention or the comparison?		The EEWG noted that the NICE Committee concluded that no recommendations should be made based on the available evidence because the potential harms associated with misinterpretation or over-interpretation of any recommendation based on the data would outweigh any benefits conferred by people being specifically informed about the data.
Type of guidance developed by EEWG	Committee Opinion	**NEW** Committee Opinion adapted from Cancer Australia that there is no conclusive evidence that having endometriosis is associated with risk of endometrial cancer.

Q3 – Timing of diagnosis and intervention

Table 67 EtD considerations for Q3 – Timing of diagnosis and intervention

Assessment	EEWG judgement	EEWG considerations
Problem Is the problem a priority?	Yes	The EEWG agreed with the NICE guideline development Committee that people with endometriosis have often experienced symptoms for a long time before they are diagnosed or treated, and this delay may have negative consequences. The aim of the review was to identify if early diagnosis and intervention is beneficial in people with suspected endometriosis. The EEWG noted that the NICE Committee had discussed the fact that no individual healthcare professional intentionally delays the diagnosis of endometriosis, but that there was nevertheless concern among patients that delays in diagnosis may be being introduced by clinicians not suspecting endometriosis until some time after initial presentation (for example because some symptoms or signs could be misinterpreted as another condition).
Desirable effects How substantial are the desirable anticipated effects?	Large	The EEWG noted that the issue of the timing of interventions was of very great importance to stakeholders and members, and might carry large health consequences. The EEWG agreed that there is potential to substantially improve outcomes if endometriosis is captured at an early stage, before end organ damage and infertility is at advanced stages.
Undesirable effects How substantial are the undesirable anticipated effects?	Large	The EEWG agreed with the NICE Committee that delay in treatment may alter the stage of the disease and result in a need to adopt different treatment options. The EEWG also acknowledged that delays in treatment could prolong suffering and have a negative impact on quality of life, including social and work interactions.
Certainty of evidence What is the overall certainty of the evidence of effects?	No new included studies	The EEWG noted that no studies were identified in the systematic review undertaken for the NICE Guideline and no studies were identified in the literature search update for the Australian Guideline. The majority of studies were excluded due to not looking at duration of symptoms as a prognostic factor. Although one recent comparative study examining the impact of diagnostic delay was identified, it was excluded due to not adjusting for confounders. The EEWG discussed that it would be difficult to design an appropriate study, which needs to be large, prospective and adjusted for confounders. The EEWG noted that it is likely that people diagnosed early had more severe symptoms so this group would be over-represented.
Values Is there important uncertainty about or variability in how much people value the main outcomes?	Probably no important uncertainty or variability	The EEWG acknowledged that systematic study of patients' values and preferences was not undertaken. However, it was agreed that people would value a timely diagnosis so that they can access appropriate treatment.
Balance of effects Does the balance between desirable and undesirable effects favour the intervention or the comparison?	Probably favours the intervention	The EEWG agreed that it was important that people diagnosed with endometriosis are treated early as a delay could result in endometriosis becoming more severe and therefore may be more harmful. The EEWG noted that the NICE Committee had pointed out that there were many reasons for a delay in diagnosis and treatment, and indeed delay was introduced at many different stages. The NICE Committee agreed that clinicians should suspect endometriosis as soon as symptoms and signs are reported at the time of first presentation. It was agreed that the guideline should promote the awareness of endometriosis and therefore speed up the recognition of the condition in the future.
Acceptability Is the intervention acceptable to key stakeholders?	Yes	
Feasibility Is the intervention feasible to implement?	Probably yes	
Type of guidance developed by EEWG	Consensus Recommendation	**ADAPTED** Consensus Recommendation **#4** from the Full NICE Guideline. For clarity and emphasis, the EEWG decided to split the NICE recommendation into two separate recommendations in the Australian Guideline. *Refer to Table App 1 for the wording of NICE recommendation.*

Q4a – Organisation of care

Table 68 EtD considerations for Q4a – Organisation of care

Assessment	EEWG judgement	EEWG considerations
Problem Is the problem a priority?	Yes	The EEWG agreed with the NICE guideline development Committee that people who suffer from endometriosis of all levels of severity will present with a wide variety of symptoms to clinicians in different settings, and the symptoms do not always correlate well with the severity of endometriosis. The EEWG agreed that it is important that people with endometriosis receive treatment in the setting that best suits their needs, symptoms and preferences. Access to specialist services was acknowledged by the EEWG to be a problem in Australia, especially in rural and remote settings. The EEWG agreed with the NICE Committee that there is currently variation in the time taken for referral to specialist services and how these services are configured to best meet people's needs.
Desirable effects How substantial are the desirable anticipated effects?	Varies	The EEWG discussed access to specialised skills as an issue in Australia, particularly away from metropolitan areas.
Undesirable effects How substantial are the undesirable anticipated effects?	Varies	The EEWG raised the issue that if there is no ability to liaise with specialists then this would present a problem.
Certainty of evidence What is the overall certainty of the evidence of effects?	No systematic review was performed	The systematic review conducted for NICE identified no relevant evidence for specialist endometriosis services. The NICE recommendations were based on expertise and discussion of the GDC and information from the health economic model that was developed for the NICE guidance. The EEWG acknowledged that the UK has established endometriosis centres, which are not available in Australia. The EEWG discussed that there is no evidence available to show whether care is better or not for people who are managed only by experts in endometriosis care.
Feasibility Is the intervention feasible to implement?		The EEWG acknowledged that the establishment of managed clinical care network and centres of expertise aligns with the National Action Plan for Endometriosis but relates to service provision and policy. This would require the support of the Commonwealth Department of Health to ensure consistency and equity of care. The EEWG discussed that the concept of centralised services in Australia for people with endometriosis aligns with the National Action Plan, but acknowledged that this would be a policy consideration for federal and state government.
Type of guidance developed by EEWG	Consensus Recommendations	**ADOPTED** Consensus Recommendation **#1** in the Full NICE Guideline. **ADAPTED** Consensus Recommendation **#2** in the Full NICE Guideline. The EEWG refocused the recommendation on the patient rather than the requirements of a gynaecological service. The EEWG changed 'Gynaecology services for women with suspected or confirmed endometriosis should have access to ' to 'People with suspected or confirmed endometriosis may require access to '. **ADAPTED** Consensus Recommendation **#3** in the Full NICE Guideline. As above, the EEWG refocused the recommendation on the patient rather than the requirements of a gynaecological service. The EEWG changed 'Specialist endometriosis services (endometriosis centres) should have access to…' to 'People with suspected or confirmed severe endometriosis may require additional services and access to…' *Refer to Table App 1 for the wording of NICE recommendations.*

Q4b – Referral to secondary care

Table 69 EtD considerations for Q4b – Referral to secondary care

Assessment	EEWG judgement	EEWG considerations
Problem Is the problem a priority?	Yes	The EEWG agreed with the NICE guideline development Committee that there is currently variation in the time taken for referral to a specialist, and the guideline should provide guidance for GPs on thresholds for further investigation and diagnosis as well as monitoring and referral. The EEWG agreed with the NICE Committee that referral should be considered based on the severity, persistence and recurrence of symptoms. If a clinical examination indicates pelvic signs of endometriosis, this should also lead to referral. The EEWG agreed that people with signs suggestive of deep endometriosis involving bowel, bladder or ureter would require further investigations, surgery or both and would need to be referred to a specialist. The EEWG agreed with the NICE Committee to not be overly prescriptive about the signs suggestive of deep endometriosis involving bowel, bladder or ureter because these could vary on a case by case basis. The EEWG also noted that there are some people who may require referral even though not suspected of having deep endometriosis. These cases could be difficult to define and there is always room for clinical judgment in decisions about referral.
Certainty of evidence What is the overall certainty of the evidence of effects?	No systematic review was performed	NICE did not conduct a separate evidence review for this question but referred to related evidence for signs and symptoms when developing recommendations for referral to secondary care.
Values Is there important uncertainty about or variability in how much people value the main outcomes?		The EEWG acknowledged that systematic study of patients' values and preferences was not undertaken and so uncertainty exists about the patient's perspective. The EEWG noted that the NICE Committee discussed patient preferences and it was highlighted that some people may choose not to have surgery. The NICE Committee agreed that these people should be considered for further monitoring because their symptoms would, most likely, persist and there may also be disease progression.
Feasibility Is the intervention feasible to implement?		While discussing this topic, the EEWG acknowledged that the UK has established endometriosis centres, which are not available in Australia. In formulating recommendations, the EEWG considered equity of access to services.
Type of guidance developed by EEWG	Consensus Recommendations	**ADAPTED** Consensus Recommendation **#9** in the Full NICE Guideline. The EEWG preferred the term 'gynaecologist' rather than 'gynaecology service', and included an additional reason for referral: 'ultrasound or imaging suggestive of higher stage or infiltrating disease' (with examples). The EEWG also changed the order of the reasons for referral to reflect the management pathway. **ADAPTED** Consensus Recommendation **#10** in the Full NICE Guideline. The EEWG changed the wording 'specialist endometriosis service (endometriosis centre)' to 'gynaecologist with an interest in endometriosis' in order to contextualise the recommendation to Australia. **ADAPTED** Consensus Recommendation **#11** in the Full NICE Guideline. The EEWG replaced reference to paediatric and adolescent gynaecology services as these are not common in Australia and it would be inequitable to recommend this. To make the recommendation more relevant to the Australian context, the EEWG referred to a 'paediatric and adolescent gynaecologist with an interest in endometriosis (depending on local service provision), or a gynaecologist who is comfortable treating adolescents with possible endometriosis'. *Refer to Table App 4 for the wording of NICE recommendations.*

Q4c – Interdisciplinary care

Table 70 EtD considerations for Q4c – Interdisciplinary care

Assessment	EEWG judgement	EEWG considerations
Problem Is the problem a priority?		The EEWG agreed that endometriosis can impact multiple facets of a patient's life and therefore interdisciplinary care may lead to improved health outcomes and patient satisfaction. The EEWG discussed what optimal care would look like for people with endometriosis, and the difference between what is meant by interdisciplinary care and multidisciplinary care.

Assessment	EEWG judgement	EEWG considerations
Certainty of evidence What is the overall certainty of the evidence of effects?	No systematic review was performed	NICE did not consider this question.
Type of guidance developed by EEWG	Committee Opinion	**NEW** Committee Opinion was developed, based on the expert opinion of EEWG members.

Q5a – Diagnosis of endometriosis

Clinical examination

Table 71 EtD considerations for Q5a – Diagnosis of endometriosis – Clinical examination

Assessment	EEWG judgement	EEWG considerations
Problem Is the problem a priority?	Yes	The EEWG agreed that it is important that people with endometriosis are assessed and a diagnosis made in a timely manner, to prevent delay in effective treatment. The EEWG discussed that clinical examination is a modality that could be conducted in primary care and resource-limited settings. The EEWG noted that the NICE Guideline did not review clinical examination as a diagnostic intervention. They also discussed that clinical examination may have been a pre-test or prior test in diagnostic studies of diagnostic imaging.
Test accuracy How accurate is the test?	Varies	The EEWG discussed that the test accuracy varies depending on the site of endometriosis and what the clinical examination entailed. Of the four studies identified in the systematic review for the Australian Guideline, one involved a detailed history focusing on intestinal symptoms and the others used digital vaginal examination with or without digital rectovaginal examination. The EEWG agreed that forest plots were not necessary for interpretation of the evidence, and that pooling would be inappropriate.
Desirable effects How substantial are the desirable anticipated effects?	Large	The EEWG agreed that an accurate test with high rates of true positives and true negatives is highly desirable and could potentially reduce diagnostic delays.
Undesirable effects How substantial are the undesirable anticipated effects?	Small	The EEWG discussed that not all people would be comfortable with clinical examination for diagnosis. It was acknowledged that it would come down to patient preference. Undesirable effects include discomfort and high rates of false negatives, particularly for diagnosis of deep infiltrating endometriosis.
Certainty of the evidence of test accuracy? What is the overall certainty of the evidence of test accuracy?	Very low	The EEWG discussed the limitations of the included studies, particularly the poor reporting, and the high risk of bias as identified using the QUADAS-2 assessment. The EEWG noted that case-control studies were excluded, as were studies that focused on indirect populations (such as all people undergoing laparoscopy) or where all people already had a diagnosis of endometriosis.
Certainty of the evidence of test's effects What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?	No included studies	The EEWG noted that no test-and-treat trials were found, therefore no clinical or patient-reported outcomes such as quality of life were identified.
Certainty of the evidence of management's effects What is the overall certainty of the evidence of effects of the management that is guided by the test results?	No included studies	The EEWG discussed that the utility of each diagnostic test was not assessed. The critical outcomes for the Australian Guideline were aligned with those in the NICE review (sensitivity, specificity and quality of life).
Certainty of the evidence of test result/management How certain is the link between test results and management decisions?	No included studies	
Certainty of effects What is the overall certainty of the evidence of effects of the test?	Very low	

Assessment	EEWG judgement	EEWG considerations
Values Is there important uncertainty about or variability in how much people value the main outcomes?	Probably no important uncertainty or variability	The EEWG acknowledged that systematic study of patients' values and preferences was not undertaken. However, the EEWG agreed that people would value an inexpensive and accurate diagnostic test for endometriosis.
Balance of effects Does the balance between desirable and undesirable effects favour the intervention or the comparison?	Favours the comparison	The EEWG discussed the lack of high quality comparative studies of diagnostic modalities. Several of the new studies included in the literature search update compared different diagnostic tests (including comparisons of clinical examination with ultrasound or MRI) but the studies were at high risk of bias. The EEWG agreed that on the basis of the available evidence, the diagnostic performance of clinical examination is not as good as imaging techniques. The EEWG discussed that clinical examination could be used as an initial examination but it has limitations, particularly in the diagnosis of DIE.
Equity What would be the impact on health equity?	Probably increased	The EEWG agreed that clinical examination could be undertaken in primary care settings and if accurate, could overcome barriers to diagnosis for people in rural and remote settings who have limited access to other diagnostic modalities.
Acceptability Is the intervention acceptable to key stakeholders?	Probably yes	The EEWG noted that patient preference would be an important consideration.
Feasibility Is the intervention feasible to implement?	Probably yes	
Type of guidance developed by EEWG	Consensus Recommendation	**NEW** Consensus Recommendation was developed following a review of the evidence on the diagnostic performance of clinical examination in diagnosing endometriosis.

Ultrasound

Table 72 EtD considerations for Q5a – Diagnosis of endometriosis – Ultrasound

Assessment	EEWG judgement	EEWG considerations
Problem Is the problem a priority?	Yes	The EEWG agreed with the deliberations of the NICE guideline development Committee that while medical treatment may be commenced empirically, it is important to be as confident as possible that the underlying diagnostic assumptions are correct and to identify any findings that require more urgent treatment. The EEWG discussed that the main imaging modalities used in diagnosing endometriosis and planning for surgery are ultrasound (abdominal, vaginal and rectal) and MRI imaging. They agreed that the 'gold standard' for diagnosis of endometriosis is considered to be laparoscopy with biopsy, which allows histological confirmation of suspicious lesions. The EEWG discussed that endometriosis might be suspected and empirically managed in primary care, but a definitive diagnosis is usually made after referral and surgery.
Test accuracy How accurate is the test?	Varies	The EEWG discussed the original evidence base identified in the NICE review and the 15 new diagnostic studies identified in the literature search update, which included studies of transvaginal ultrasound, transvaginal ultrasound plus transabdominal ultrasound, and rectal scanning. The EEWG discussed concerns raised by the evidence reviewers for the Australian Guideline about the ability to undertake meta-analyses and synthesise the entire body of evidence, given limitations in time and budget. The EEWG agreed that the extensive analyses undertaken in the NICE review (including ROC plots and meta-analysis of sensitivity and specificity) were not feasible and that forest plots should be restricted to studies of ultrasound where 2x2 data were available (NICE only included studies where 2x2 data were reported). The EEWG agreed that forest plots were particularly helpful to illustrate the variation in sensitivity and specificity between studies and across endometriosis sites. The EEWG noted that the clinical evidence in the review referred to studies from specialist and not community settings. In a community setting, many ultrasonographers have a general ultrasound certification, rather than specialist expertise in reviewing endometriosis. The EEWG agreed with the NICE Committee that this is likely to influence the accuracy of diagnosis and discussed how results of imaging need to be interpreted in light of the practitioner's level of training. The EEWG also discussed that the evidence available was drawn from testing the different endometriosis sites. They agreed with the interpretation of the NICE Committee that overall the specificity was consistently high, however the sensitivity was heterogeneous. The evidence showed that a well performed ultrasound scan (in a specialist centre) accurately identified site specific

Assessment	EEWG judgement	EEWG considerations
		endometriosis (for example, endometrioma, rectovaginal and rectocervical disease), but where endometriosis is superficial and spread across different sites throughout the pelvis it is less accurate. The EEWG agreed with the NICE Committee that a negative ultrasound does not guarantee endometriosis is absent and if symptoms persist, further investigation should be considered. The EEWG noted the conclusions of the NICE Committee that in addition to changes in technology, training of the practitioner could also impact on imaging results, as well as the quality of the examination itself. However, it was agreed that the training of healthcare professionals was outside the scope of the guideline.
Desirable effects How substantial are the desirable anticipated effects?	Large	The EEWG agreed with the NICE Committee that the consequences of testing are of great importance to people and delay in diagnosis of endometriosis due to false negative results is a well-recognised issue in this population. Not having a diagnosis, or having an incorrect negative diagnosis, can cause emotional distress. The EEWG agreed that a correct positive diagnosis of endometriosis may provide relief for people and improve their emotional wellbeing, whereas a correct negative diagnosis establishes that a person's symptoms are not due to endometriosis and enables the opportunity to promptly pursue investigation for other causes.
Undesirable effects How substantial are the undesirable anticipated effects?	Moderate	The EEWG acknowledged the negative impact of false positive and false negative test results.
Certainty of the evidence of test accuracy? What is the overall certainty of the evidence of test accuracy?	Very low	The EEWG discussed the available evidence base, noting that the NICE review included studies published prior to 2003, which would have used older ultrasound technology that may not be used in current practice. The EEWG discussed that many of the older studies would have focused on imaging of hard tissue, whereas more recent studies focus on soft tissue imaging because of the advancement in technology. The EEWG noted that case-control studies were excluded as per the research protocol, as were studies that focused on indirect populations (such as all people undergoing laparoscopy) or where all people already had a diagnosis of endometriosis. The EEWG discussed that for some studies of deep infiltrating endometriosis and endometriosis outside the uterus, the distinction between diagnosis and surgical planning (to map the location of lesions) was unclear. The EEWG agreed with the NICE Committee that the certainty of the evidence is very low, even after consideration of the new studies identified in the search update. This was mainly due to risk of bias (often the patient selection was not consecutive or random, not all patients were included in the analysis or studies were not blinded), inconsistency (particularly in relation to sensitivity estimates) and imprecision (with a high level of uncertainty as indicated by the wide confidence intervals). The EEWG noted that confidence intervals were not reported in all publications and that 2x2 data were missing from a large number of the newly identified studies, limiting the ability to verify information and to pool results. The EEWG also noted differences in the terminology of defining endometriosis sites, for example, posterior pelvic endometriosis as a term used by clinicians, but which may refer to many sites.
Certainty of the evidence of test's effects What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?	No included studies	The EEWG noted that no test-and-treat trials were found, therefore no clinical or patient-reported outcomes such as quality of life were identified.
Certainty of the evidence of management's effects What is the overall certainty of the evidence of effects of the management that is guided by the test results?	No included studies	The EEWG discussed that the utility of each diagnostic test was not assessed. The critical outcomes for the Australian Guideline were aligned with those in the NICE review (sensitivity, specificity and quality of life).
Certainty of the evidence of test result/management How certain is the link between test results and management decisions?	No included studies	
Certainty of effects What is the overall certainty of the evidence of effects of the test?	Very low	

Assessment	EEWG judgement	EEWG considerations
Values Is there important uncertainty about or variability in how much people value the main outcomes?	Probably no important uncertainty or variability	The EEWG acknowledged that systematic study of patients' values and preferences was not undertaken. However, the EEWG agreed that people would value an accurate, non-invasive diagnostic test for endometriosis. Sensitivity and specificity were considered proxies for patient outcomes (indicating a benefit from a true negative or true positive finding).
Balance of effects Does the balance between desirable and undesirable effects favour the intervention or the comparison?		The EEWG noted that the NICE review did not include any comparative evidence of diagnostic modalities as it was not specified in the Protocol. Several of the new studies included in the literature search update compared different diagnostic tests (including comparisons of ultrasound with clinical examination or CT or MRI) but the studies were all at high risk of bias and the updated literature search was only from 2016 onwards for ultrasound. The EEWG agreed that ultrasound is preferable to other imaging modalities for the investigation of suspected endometriosis. However, due to a lack of high quality comparative evidence, no firm conclusions can be drawn about comparative diagnostic performance.
Equity What would be the impact on health equity?	Probably increased	The EEWG noted that specialists in gynaecological ultrasound may not be as accessible in rural and remote settings.
Acceptability Is the intervention acceptable to key stakeholders?	Yes	
Feasibility Is the intervention feasible to implement?	Yes	The EEWG discussed that GPs usually refer people to a local imaging services and will not know where to find healthcare professionals have specialist expertise in gynaecological imaging. The EEWG discussed the need for specialist pathways for O&Gs to undertake imaging, and for the upskilling of radiologists and sonographers, particularly in relation to deep endometriosis. The EEWG also discussed the need for quality improvements in imaging for endometriosis and a standard for reporting, and agreed that this should be included as a statement in the narrative.
Type of guidance developed by EEWG	Evidence-based Recommendations and Consensus Recommendation	**ADAPTED** Evidence-based Recommendation **#17** in the Full NICE Guideline. The EEWG added CT to the list of potential diagnostic modalities. **ADAPTED** Evidence-based Recommendation **#18** in the Full NICE Guideline. The EEWG split the recommendation so that transvaginal ultrasound for initial investigation is split out from specialised ultrasound to determine the extent of deep endometriosis. **ADOPTED** Evidence-based Recommendation **#19** in the Full NICE Guideline. *Refer to Table App 5 for the wording of NICE recommendations.* **NEW** Consensus Recommendation was developed by the EEWG to acknowledge that ideally/optimally, interpretation of specialised ultrasound for deep endometriosis would be done by a healthcare practitioner with specialist expertise in gynaecological imaging.

Computed tomography

Table 73 EtD considerations for Q5a – Diagnosis of endometriosis – CT

Assessment	EEWG judgement	EEWG considerations
Problem Is the problem a priority?	Yes	See earlier diagnostic modalities for EEWG considerations on diagnostic testing. The EEWG discussed that CT is not usually requested in Australia for diagnosis of endometriosis but is used for suspected ureteric disease.
Test accuracy How accurate is the test?	Don't know	The EEWG discussed the limitations in the nine studies identified in the literature search and the variability in the CT techniques used across studies. The EEWG noted that CT was not a diagnostic modality included in the NICE review.
Desirable effects How substantial are the desirable anticipated effects?	Large	As for other diagnostic modalities, the EEWG agreed that accurate diagnosis of endometriosis is highly desirable.
Undesirable effects How substantial are the undesirable anticipated effects?	Small	The EEWG noted that irradiation is an issue, particularly for young people.

Assessment	EEWG judgement	EEWG considerations
Certainty of the evidence of test accuracy? What is the overall certainty of the evidence of test accuracy?	Very low	The EEWG noted that nine relevant diagnostic studies were identified and all were judged to be at high risk of bias. Confidence intervals were reported in only two of the included studies. Five studies (all from Italy) reported 2x2 data (in tables or text) but the size of these studies was generally small (ranging from 33 to 103 subjects). The certainty of the evidence base was very low according to GRADE. The EEWG agreed that forest plots were not necessary for interpretation. The EEWG noted that case-control studies were excluded as per the research protocol, as were studies that focused on indirect populations (such as all people undergoing laparoscopy) or where all people already had a diagnosis.
Certainty of the evidence of test's effects What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?	No included studies	The EEWG noted that no test-and-treat trials were found, therefore no clinical or patient-reported outcomes such as quality of life were identified.
Certainty of the evidence of management's effects What is the overall certainty of the evidence of effects of the management that is guided by the test results?	No included studies	
Certainty of the evidence of test result/management How certain is the link between test results and management decisions?	No included studies	
Certainty of effects What is the overall certainty of the evidence of effects of the test?	Very low	
Values Is there important uncertainty about or variability in how much people value the main outcomes?	Probably no important uncertainty or variability	The EEWG acknowledged that systematic study of patients' values and preferences was not undertaken. However, the EEWG agreed that people would value an accurate, non-invasive diagnostic test for endometriosis.
Balance of effects Does the balance between desirable and undesirable effects favour the intervention or the comparison?	Does not favour either the intervention or the comparison	The EEWG noted that several of the new studies included in the literature search update compared different diagnostic tests (including comparisons of CT with ultrasound or MRI) but the studies were at high risk of bias. The EEWG agreed that due to a lack of high quality comparative evidence, no firm conclusions can be drawn about comparative diagnostic performance but the harms of CT (irradiation) need to be considered, especially in young people.
Equity What would be the impact on health equity?	Probably increased	The EEWG noted that CT may not be as accessible in rural and remote settings.
Acceptability Is the intervention acceptable to key stakeholders?	Probably yes	
Feasibility Is the intervention feasible to implement?	Probably yes	
Type of guidance developed by EEWG	Consensus Recommendations	**NEW** Consensus Recommendations (three in total) were developed by the EEWG following a review of the evidence on the diagnostic performance of CT in diagnosing endometriosis.

Magnetic resonance imaging

Table 74 EtD considerations for Q5a – Diagnosis of endometriosis – MRI

Assessment	EEWG judgement	EEWG considerations
Problem Is the problem a priority?	Yes	See earlier diagnostic modalities for EEWG considerations on diagnostic testing. The EEWG agreed with the NICE guideline development Committee that the main imaging modalities used in diagnosing and mapping endometriosis are ultrasound (abdominal, vaginal and rectal) and MRI imaging.

Assessment	EEWG judgement	EEWG considerations
Test accuracy How accurate is the test?	Varies	The EEWG discussed the original evidence base identified in the NICE review and the 8 new diagnostic studies identified in the literature search update. The EEWG noted that a literature search cut-off date was not specified in the NICE review and studies from 1990 or earlier would have used MRI scanning techniques that may not be used in current practice due to advancement of technology. The EEWG noted that the evidence available was drawn from testing across different endometriosis sites. The EEWG noted that the NICE Committee had discussed that specificity was particularly variable across studies and there was a high level of imprecision expressing uncertainty around the pooled effect estimates. The EEWG noted that the NICE Committee considered that their recommendations should not extend to earlier or more superficial disease because the evidence was limited to the detection of deep infiltrating endometriosis. The EEWG agreed with the NICE Committee that the evidence showed that MRI was a good test for deep endometriosis but should not be used as the first diagnostic or investigative test in people with suspected endometriosis. The EEWG agreed with the NICE Committee that due to the large number of false negative results, a recommendation to use MRI testing may potentially lead to many people being falsely reassured that they do not have endometriosis. The NICE Committee therefore discounted MRI as a first line test and the recommendations regarding its use were limited to the diagnosis of deep endometriosis infiltrating the bowel, bladder or ureter in people with more advanced stages of the disease, who may require further surgery.
Desirable effects How substantial are the desirable anticipated effects?	Large	The EEWG agreed that MRI is a non-invasive test for the diagnosis of endometriosis and, if it is accurate, it could lead to the diagnosis without the need for a surgical procedure or it could decrease the need for it.
Undesirable effects How substantial are the undesirable anticipated effects?	Large	The EEWG acknowledged that specificity was particularly variable across studies and a negative
Certainty of the evidence of test accuracy? What is the overall certainty of the evidence of test accuracy?	Very low	The EEWG noted that the quality of the evidence was very low according to GRADE criteria. This was mainly due to risk of bias (often the patient selection was not consecutive or random, or not all patients were included in the analysis), inconsistency (particularly specificity estimates), as well as imprecision (indicated by the confidence region in the pooled analysis conducted for NICE). The EEWG noted that confidence intervals were not reported in all publications and that 2x2 data were missing from 6 of the 8 new studies identified in the literature search update, limiting the ability to verify information and to pool results. The EEWG agreed that forest plots were not necessary for interpretation of the evidence. The EEWG noted that case-control studies were excluded as per the research protocol, as were studies that focused on indirect populations (such as all people undergoing laparoscopy) or where all people already had a diagnosis of endometriosis. The EEWG discussed that for some studies of deep infiltrating endometriosis and endometriosis outside the uterus, the distinction between diagnosis and surgical planning (to map the location of lesions) was unclear.
Certainty of the evidence of test's effects What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?	No included studies	The EEWG noted that no test-and-treat trials were found, therefore no clinical or patient-reported outcomes such as quality of life were identified.
Certainty of the evidence of management's effects What is the overall certainty of the evidence of effects of the management that is guided by the test results?	No included studies	
Certainty of the evidence of test result/management How certain is the link between test results and management decisions?	No included studies	
Certainty of effects What is the overall certainty of the evidence of effects of the test?	Very low	

Assessment	EEWG judgement	EEWG considerations
Values Is there important uncertainty about or variability in how much people value the main outcomes?	Probably no important uncertainty of variability	The EEWG acknowledged that systematic study of patients' values and preferences was not undertaken. However, the EEWG agreed that people would value an accurate, non-invasive diagnostic test for endometriosis.
Balance of effects Does the balance between desirable and undesirable effects favour the intervention or the comparison?	Does not favour either the intervention or the comparison	The EEWG agreed that due to a lack of high quality comparative evidence, no firm conclusions can be drawn about comparative diagnostic performance. The EEWG noted that the NICE review did not include any comparative evidence of diagnostic modalities as it was not specified in their Protocol. Several of the new studies included in the literature search update compared different diagnostic tests (including comparisons of MRI with ultrasound or clinical examination or CT) but the studies were at high risk of bias and the updated literature search was only from 2016 onwards for MRI. The EEWG discussed the relative benefits and harms associated with MRI scanning. The EEWG agreed with the NICE Committee that laparoscopy, although invasive, is necessary as the gold standard test for identification of endometriosis; the benefit of MRI would be as an additional non-invasive informative test for surgery because it would identify the involvement and depth of endometriosis prior to surgery. The EEWG also agreed that if a person suspected of having endometriosis had a negative MRI, endometriosis could not be ruled out as there was no certainty that these people would not have endometriosis and further investigation would need to be considered if symptoms persisted. The EEWG agreed that the value of an MRI was dependent on the proper interpretation and reporting of the results and that this should be performed by a healthcare professional appropriately trained in interpretation of MRI scans for endometriosis.
Equity What would be the impact on health equity?	Probably reduced	The EEWG acknowledged that there is no Medicare rebate for MRI for endometriosis.
Acceptability Is the intervention acceptable to key stakeholders?	Probably yes	The EEWG discussed that MRI would probably be an acceptable option, especially for people who cannot have an ultrasound.
Feasibility Is the intervention feasible to implement?	Probably yes	
Type of guidance developed by EEWG	Evidence-based Recommendations	**ADOPTED** Evidence-based Recommendation **#22** in the Full NICE Guideline. **ADOPTED** Evidence-based Recommendation **#23** in the Full NICE Guideline. **ADAPTED** Evidence-based Recommendation **#24** in the Full NICE Guideline. The EEWG changed 'ensure that' because this would create an equity of access issue. *Refer to Table App 5 for the wording of NICE recommendations.*

Biomarkers

Table 75 EtD considerations for Q5a – Diagnosis of endometriosis – Biomarkers

Assessment	EEWG judgement	EEWG considerations
Problem Is the problem a priority?	Yes	The EEWG agreed that a non-invasive diagnostic test is desirable.
Test accuracy How accurate is the test?	Inaccurate	The EEWG considered the evidence presented in the NICE Guideline together with the two new studies identified in the literature search update for the Australian Guideline. The NICE review identified one Cochrane review (25 diagnostic studies of CA125), one small study of HE-4, and one Cochrane Review (8 diagnostic studies) of the nerve fibre marker Protein Gene Product 9.5 (PGP 9.5). The two new studies assessed serum CA125. The EEWG noted comments from the NICE guideline development Committee that serum CA125 may not be a sensitive marker, but a positive result will indicate people who truly have endometriosis. However, in current practice, people would not be diagnosed based on CA125 testing alone; if they had signs and symptoms and an incidentally raised CA125 levels, they would usually be referred for further diagnostic procedures. The EEWG agreed with the NICE Committee that this test does not add anything to the diagnostic strategy, apart from a possible delay and additional costs for further unnecessary referral and investigation.
Desirable effects How substantial are the desirable anticipated effects?	Large	The EEWG discussed that numerous biomarkers have been proposed and if these prove to be sufficiently accurate, a blood test could provide a safer and cheaper method of diagnosis that is accessible in primary care.

Assessment	EEWG judgement	EEWG considerations
Undesirable effects How substantial are the undesirable anticipated effects?	Moderate	The EEWG agreed that the anticipated harmful effects are moderate because of the low sensitivity of biomarker testing. The EEWG noted that the NICE guideline development Committee had discussed the impacts of a false negative diagnosis, which could result in the person not receiving effective management and the potential additional negative psychological impact of a false negative diagnosis if a person was experiencing painful symptoms. They also noted that a false positive result might lead to unnecessary treatment (and associated costs) and also result in a negative psychological impact.
Certainty of the evidence of test accuracy? What is the overall certainty of the evidence of test accuracy?	Very low	The EEWG considered the evidence presented in the NICE Guideline together with the two new studies identified in the literature search update for the Australian Guideline. For CA125, the quality of the evidence was very low according to GRADE criteria, mainly due to risk of bias (often the patient selection was not consecutive or random, not all patients were included in the analysis or the serum CA125 cut-off was not pre-specified) and inconsistency (particularly related to sensitivity estimates).
Certainty of the evidence of test's effects What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?	No included studies	The EEWG noted that no test-and-treat trials were found, therefore no clinical or patient-reported outcomes such as quality of life were identified.
Certainty of the evidence of management's effects What is the overall certainty of the evidence of effects of the management that is guided by the test results?	No included studies	
Certainty of the evidence of test result/management How certain is the link between test results and management decisions?	No included studies	
Certainty of effects What is the overall certainty of the evidence of effects of the test?	Very low	
Values Is there important uncertainty about or variability in how much people value the main outcomes?	Probably no important uncertainty or variability	The EEWG acknowledged that systematic study of patients' values and preferences was not undertaken. However, the EEWG agreed that people would value an accurate, non-invasive diagnostic test for endometriosis.
Balance of effects Does the balance between desirable and undesirable effects favour the intervention or the comparison?	Favours the comparison	The EEWG agreed that CA125 does not add anything to the diagnostic strategy, apart from a possible delay and additional costs for further unnecessary referral and investigation. The EEWG noted the conclusions from the NICE Committee that the serum CA125 test would have too many false negative results to promote usage in clinical practice. The EEWG agreed with the NICE Committee that further evidence on CA125 as a diagnostic biomarker is unlikely to reduce the uncertainty around the results; there are many studies that have investigated the diagnostic accuracy of serum CA125 with a fairly consistent pattern of low sensitivity. The EEWG agreed with the NICE Committee to not prioritise this topic for further research. The EEWG agreed with the conclusions of the NICE Committee that there was no evidence to support a recommendation for HE-4 for the diagnosis of endometriosis or endometrioma in people with suspected endometriosis. The EEWG noted that the NICE Committee decided not to make a recommendation or a research recommendation based on their discussion about PGP 9.5, mainly due to the fact that this methodology in not specific as a diagnostic tool to detect endometriosis. The EEWG agreed with the NICE Committee that as a method of testing, PGP 9.5 requires standardisation in methodology, it is not routinely used in current practice, it is not conclusively validated and utilised in most laboratories and is expensive.
Equity What would be the impact on health equity?	Probably no impact	
Acceptability Is the intervention acceptable to key stakeholders?	Probably yes	The EEWG agreed that if a blood test could accurately diagnose endometriosis, it would probably be acceptable but might lead to further investigations to determine the extent of disease.

Assessment	EEWG judgement	EEWG considerations
Feasibility Is the intervention feasible to implement?	Yes	
Type of guidance developed by EEWG	Consensus Recommendations	**ADOPTED** Consensus Recommendation **#20** in the Full NICE Guideline. **ADOPTED** Consensus Recommendation **#21** in the Full NICE Guideline. *Refer to Table App 5 for the wording of NICE recommendations.*

Surgical diagnosis

Table 76 EtD considerations for Q5a – Diagnosis of endometriosis – Surgical diagnosis

Assessment	EEWG judgement	EEWG considerations
Problem Is the problem a priority?	Yes	See earlier diagnostic modalities for EEWG considerations on diagnostic testing. The EEWG noted that laparoscopy is the 'gold standard' for making a diagnosis of endometriosis but there is clinical disagreement about the need for a histological specimen to confirm the visual diagnosis.
Test accuracy How accurate is the test?	Accurate	The EEWG considered the evidence presented in the NICE Guideline. No studies were identified in the literature search update for the Australian Guideline. Of the 17 studies included in the NICE review, 3 studies reported sensitivity and specificity, whereas the remaining 14 studies reported positive test results only (i.e. biopsy histology results from only those who were laparoscopically diagnosed with endometriosis). The EEWG agreed with the NICE guideline development Committee that a negative finding following a thorough laparoscopic visualisation is highly specific and patients can be reassured that they do not have endometriosis. However, histological examination of biopsied tissue is considered to be a gold standard test and helpful to confirm the visual diagnosis; it is also required to exclude malignancy if ovarian endometriosis (endometrioma) is fenestrated and ablated.
Desirable effects How substantial are the desirable anticipated effects?	Large	
Undesirable effects How substantial are the undesirable anticipated effects?	Moderate	
Certainty of the evidence of test accuracy? What is the overall certainty of the evidence of test accuracy?	Very low	The EEWG noted that the evidence identified in the NICE review could not be pooled due to the differences in study design and how results were reported; the results are reported in the Full NICE Guideline by study. The EEWG noted that risk of bias was very high to moderate according to QUADAS 2 criteria. Main reasons leading to downgrading of evidence shared by the majority of studies were no information on blinding and it was unclear whether patients were selected consecutively or randomly. The EEWG noted the NICE Committee comment that it is highly likely that in some papers included in the review, where the visual surgical diagnosis of endometriosis was often not confirmed by histology, the researchers did not look hard enough to find the condition. They also believed that if a person had a visual diagnosis of endometriosis, it would not be always be confirmed by histology. On this basis, the NICE Committee agreed that having a histology report is very useful for the patient as it may offer more reassurance.
Certainty of the evidence of test's effects What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?	No included studies	The EEWG noted that no test-and-treat trials were found, therefore no clinical or patient-reported outcomes such as quality of life were identified.
Certainty of the evidence of management's effects What is the overall certainty of the evidence of effects of the management that is guided by the test results?	No included studies	

Assessment	EEWG judgement	EEWG considerations
Certainty of the evidence of test result/management How certain is the link between test results and management decisions?	No included studies	
Certainty of effects What is the overall certainty of the evidence of effects of the test?	Very low	
Values Is there important uncertainty about or variability in how much people value the main outcomes?	Important uncertainty or variability	The EEWG acknowledged that systematic study of patients' values and preferences was not undertaken and so uncertainty exists about the patient's perspective. The EEWG discussed that there are false negatives with substantial disease and false positives based on visual diagnosis without histology.
Balance of effects Does the balance between desirable and undesirable effects favour the intervention or the comparison?	Probably favours the intervention	The NICE Committee discussed whether it is practical to perform histology to diagnose endometriosis and concluded that histology may be important in order to diagnose other conditions and/or malignancies. In terms of endometrioma, the NICE Committee agreed that surgical treatment of endometrioma should include histology to rule out an alternative diagnosis of ovarian lesions and to exclude malignancies, and that it is a good practice, when undertaking laparoscopic excision, to send excised tissue for histology. The EEWG noted concerns from the NICE Committee that laparoscopies are sometimes performed with inadequate examination of the pelvis resulting in false negative results and agreed that there should be a systematic examination of the pelvis. It was agreed that this systematic inspection should be carried out by a gynaecologist with training and skills in laparoscopic surgery because it is possible to miss significant endometriosis.
Equity What would be the impact on health equity?		
Acceptability Is the intervention acceptable to key stakeholders?	Yes	The EEWG discussed that there is a large number of first and repeat surgeries each year in Australia for endometriosis. Surgery is acceptable to people with endometriosis and clinicians although there is a risk associated with it.
Feasibility Is the intervention feasible to implement?	Yes	
Type of guidance developed by EEWG	Consensus Recommendations	**ADAPTED** Evidence-based Recommendation **#25** in the Full NICE Guideline. The EEWG added 'and treat' to the wording of the recommendation to reflect that laparoscopy could be considered for diagnosis and treatment. **ADAPTED** Consensus Recommendation **#26** in the Full NICE Guideline. The EEWG added 'detailed' before pelvic ultrasound. **ADAPTED** Evidence-based Recommendation **#27** in the Full NICE Guideline. The EEWG clarified that the recommendation refers to laparoscopy 'for suspected endometriosis'. The EEWG also expanded the systematic inspection to the pelvis 'and abdomen'. **ADAPTED** Evidence-based Recommendation **#28** in the Full NICE Guideline. The EEWG clarified in the recommendation that a biopsy could be considered in cases where no visible disease is apparent and also in cases where disease is apparent. **ADAPTED** Evidence-based Recommendation **#29** in the Full NICE Guideline. The EEWG amended some of the wording for clarity. *Refer to Table App 5 for the wording of NICE recommendations.*

Q5b – Diagnosis of adenomyosis

Ultrasound

Table 77 EtD considerations for Q5b – Diagnosis of adenomyosis – Ultrasound

Assessment	EEWG judgement	EEWG considerations
Problem Is the problem a priority?	Yes	The EEWG noted that a diagnostic delay of 5-10 years is not unusual for endometriosis and agreed that the delay in diagnosis for adenomyosis may be of similar duration. The EEWG discussed that ultrasound is commonly used to diagnose adenomyosis but the technique is not standardised there is no consensus on specific diagnostic criteria for adenomyosis. The EEWG also discussed the lack of agreed histological criteria for diagnosis of adenomyosis, which impacts on the use of histology as a reference standard for assessing diagnostic performance of imaging techniques. The EEWG noted that there is not a clear relationship between the symptoms of adenomyosis and diagnostic findings. Members agreed that just because adenomyosis is diagnosed on ultrasound, it does not need to be treated if asymptomatic. The EEWG discussed that about one-third of people with adenomyosis are asymptomatic. It was also noted that if adenomyosis is present, it is likely that the person may also have endometriosis.
Test accuracy How accurate is the test?	Don't know	The EEWG discussed the two included studies and agreed that test accuracy is difficult to determine from these studies. One study from Russia examined the addition of shear wave elastography to transvaginal scan but study subjects also had a transabdominal scan. The second study from Egypt compared transvaginal ultrasound with a combination of transvaginal ultrasound followed by office hysteroscopy-guided endomyometrial biopsy. The EEWG agreed that interpretation of any study is hampered by lack of agreed histological criteria for adenomyosis.
Desirable effects How substantial are the desirable anticipated effects?	Large	The EEWG agreed that an accurate test with high rates of true positives and true negatives is highly desirable and could potentially reduce diagnostic delays.
Undesirable effects How substantial are the undesirable anticipated effects?	Large	The EEWG discussed the negative impact of high rates of false positives and false negatives.
Certainty of the evidence of test accuracy? What is the overall certainty of the evidence of test accuracy?	Low to very low	The EEWG noted the overarching issues related to the diagnostic definition.
Certainty of the evidence of test's effects What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?	No included studies	The EEWG noted that no test-and-treat trials were found, therefore no clinical or patient-reported outcomes such as quality of life were identified.
Certainty of the evidence of management's effects What is the overall certainty of the evidence of effects of the management that is guided by the test results?	No included studies	
Certainty of the evidence of test result/management How certain is the link between test results and management decisions?	Don't know	
Certainty of effects What is the overall certainty of the evidence of effects of the test?	Low	
Values Is there important uncertainty about or variability in how much people value the main outcomes?	No important uncertainty or variability	The EEWG acknowledged that systematic study of patients' values and preferences was not undertaken and so uncertainty exists about the patient's perspective. However, the EEWG agreed that people would value non-invasive tests that are accurate.

Assessment	EEWG judgement	EEWG considerations
Balance of effects Does the balance between desirable and undesirable effects favour the intervention or the comparison?	Favours the intervention	The EEWG discussed that ultrasound is a preferable diagnostic intervention because it is less invasive than biopsy or histological confirmation at surgery.
Resources required How large are the resource requirements (costs)?	Don't know	The EEWG agreed not to include review of cost or cost-effectiveness when developing the Australian Guidelines.
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?	Not reviewed	As above
Cost effectiveness Does the cost-effectiveness of the intervention favour the intervention or the comparison?	Not reviewed	As above
Equity What would be the impact on health equity?		The EEWG discussed that Certificate of Obstetrical and Gynaecological Ultrasound (COGU) groups may have higher diagnostic specificity, although this is anecdotal. There may be differences across settings, for example in rural settings compared with metropolitan tertiary units.
Acceptability Is the intervention acceptable to key stakeholders?	Yes	The EEWG agreed that accurate, non-invasive tests would be welcomed.
Feasibility Is the intervention feasible to implement?	Yes	
Type of guidance developed by EEWG	Evidence-based Recommendation	**NEW** Evidence-based Recommendation was developed by the EEWG following a review of the published evidence from 2009 onwards on the diagnostic performance of ultrasound in diagnosing adenomyosis.

Magnetic resonance imaging

Table 78 EtD considerations for Q5b – Diagnosis of adenomyosis – MRI

Assessment	EEWG judgement	EEWG considerations
Problem Is the problem a priority?	Yes	The EEWG discussed the need for a non-invasive diagnostic technique in people who could not undergo ultrasound.
Test accuracy How accurate is the test?	Don't know	The EEWG noted that no studies were identified that met the eligibility criteria.
Desirable effects How substantial are the desirable anticipated effects?		The EEWG agreed that an accurate test with high rates of true positives and true negatives is highly desirable.
Undesirable effects How substantial are the undesirable anticipated effects?		The EEWG agreed that high rates of false positives and false negatives are undesirable.
Certainty of the evidence of test accuracy? What is the overall certainty of the evidence of test accuracy?	No included studies	The EEWG noted that no studies were identified that met the eligibility criteria. The EEWG agreed that diagnostic studies are required, particularly head to head studies of ultrasound versus MRI versus histological confirmation.
Certainty of the evidence of test's effects What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?	No included studies	

Assessment	EEWG judgement	EEWG considerations
Certainty of the evidence of management's effects What is the overall certainty of the evidence of effects of the management that is guided by the test results?	No included studies	
Certainty of the evidence of test result/management How certain is the link between test results and management decisions?	Don't know	
Certainty of effects What is the overall certainty of the evidence of effects of the test?	No included studies	
Values Is there important uncertainty about or variability in how much people value the main outcomes?	Probably no important uncertainty or variability	The EEWG acknowledged that systematic study of patients' values and preferences was not undertaken and so uncertainty exists about the patient's perspective. However, the EEWG agreed that people would value non-invasive tests that are accurate.
Balance of effects Does the balance between desirable and undesirable effects favour the intervention or the comparison?	Don't know	
Resources required How large are the resource requirements (costs)?	Varies	The EEWG noted that MRI costs more than ultrasound.
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?	No included studies	The EEWG agreed not to include review of cost or cost-effectiveness when developing the Australian Guidelines.
Cost effectiveness Does the cost-effectiveness of the intervention favour the intervention or the comparison?	No included studies	As above
Equity What would be the impact on health equity?		
Acceptability Is the intervention acceptable to key stakeholders?	Probably yes	The EEWG agreed that MRI would probably be acceptable to people who could not have an ultrasound.
Feasibility Is the intervention feasible to implement?	Probably yes	
Type of guidance developed by EEWG	Consensus Recommendation	**NEW** Consensus Recommendation was developed by the EEWG following a review of the published evidence from 2009 onwards on the diagnostic performance of MRI in diagnosing adenomyosis. No relevant studies were identified.

Q6 – Systems that can guide treatment

Table 79 EtD considerations for Q6 – Systems that can guide treatment

Assessment	EEWG judgement	EEWG considerations
Problem Is the problem a priority?	Probably yes	The EEWG agreed with the NICE guideline development Committee that a number of classification systems have been developed for staging endometriosis and are in use, but that the effectiveness of using endometriosis-staging systems to guide treatment of endometriosis is unclear. The EEWG discussed that staging systems could be useful in endometriomas, for example, to measure recurrence rate and ovarian reserve. The EEWG discussed that if a reliable staging system was available it could potentially address the problem.
Desirable effects How substantial are the desirable anticipated effects?	Moderate	The EEWG discussed that if a reliable staging system that correlated stage with severity of pain and disease was available, the desirable effects could be graded higher than moderate.
Undesirable effects How substantial are the undesirable anticipated effects?	Varies	The EEWG discussed potential undesirable effects such as mis-staging a person with endometriosis.
Certainty of evidence What is the overall certainty of the evidence of effects?	No included studies	The EEWG noted that the systematic review for NICE found no relevant studies that compared the use of any staging system with other staging systems or with not using a staging system. The NICE Committee concluded that there is not enough evidence to show the effectiveness of using staging systems to guide treatment of pain associated with endometriosis, and agreed that treatment decisions need to be based on the symptoms and be tailored to individual needs, preferences and priorities in terms of pain and fertility preservation. The EEWG noted that no additional research matching the detailed PICO inclusion criteria was identified in the literature search update. The EEWG discussed that assessment of fertility in people with endometriosis and therefore the staging in relation to fertility was outside the scope of the NICE guideline. Although systems that are specific to fertility were among the eligible interventions for this question, the critical outcomes were pain, quality of life, and effect on daily activities. The EEWG discussed that the EFI has been validated in multiple studies as being reproducible and accurate, but the effectiveness of fertility systems for predicting pregnancy outcome was not specified in the PICO. The EEWG noted and agreed with the decision from the NICE Committee not to propose a research recommendation relating to staging systems. The NICE Committee discussed that it would always be difficult to have an agreed system that would classify people with endometriosis to one particular treatment choice; the treatment strategy would always need to be tailored to the individual person and their priorities and preferences rather than to a particular stage of the condition.
Values Is there important uncertainty about or variability in how much people value the main outcomes?	Unclear	The EEWG noted that how much people might value a reliable staging system is difficult to answer. The EEWG acknowledged that systematic study of patients' values and preferences was not undertaken and so uncertainty exists about the patient's perspective.
Balance of effects Does the balance between desirable and undesirable effects favour the intervention or the comparison?	Don't know	The EEWG noted that the stage of endometriosis as assessed using staging systems does not correlate with severity of disease or symptoms; as such, the balance of effects between desirable and desirable cannot be quantified.
Acceptability Is the intervention acceptable to key stakeholders?	Don't know	The EEWG noted that the acceptability of staging systems is presently unclear. If there was a reliable staging system that was predictive of outcome, this would be supported by members and might be acceptable to other stakeholders.
Feasibility Is the intervention feasible to implement?	Probably yes	The EEWG agreed that if staging systems worked well, they would be easy to implement. The EEWG discussed factors such as co-morbid conditions like myofascial pain. The EEWG discussed that the NECST data dictionary has been developed and would provide consistency in reporting, which would be useful.
Type of guidance developed by EEWG	Consensus Recommendations	**ADAPTED** Consensus Recommendation **#30** from the Full NICE Guideline. The EEWG considered the existing NICE recommendation to be generally acceptable but added factors to consider. **ADAPTED** Consensus Recommendation **#31** from the Full NICE Guideline. The EEWG considered the existing NICE recommendation to be generally acceptable but included that documentation should be in line with the NECST Registry data dictionary. *Refer to Table App 6 for the wording of NICE recommendations.*

Q7a – Pharmacological management – Analgesics

Table 80 EtD considerations for Q7a – Pharmacological management – Analgesics

Assessment	EEWG judgement	EEWG considerations
Problem Is the problem a priority?	Yes	The EEWG agreed that pain management is a high priority problem for people with suspected or confirmed endometriosis or adenomyosis. The EEWG discussed that symptoms associated with endometriosis differ with each person; however, pain (whether it be pelvic pain, painful periods, pain on intercourse, pain on urination or on defecation) is almost always a factor. The EEWG agreed with the NICE guideline development Committee that the level of pain experienced does not always relate to the extent of the disease and minor disease can be as or more painful than severe disease. It is often related to the location of the disease. The EEWG discussed that analgesia can only provide symptomatic relief of pain, rather than addressing any underlying pathology, but that effective pain relief can provide an alternative to surgery.
Desirable effects How substantial are the desirable anticipated effects?	Moderate	The EEWG estimated the desirable effect of analgesics to be moderate as analgesics aren't targeting the pathology (i.e. the underlying cause of the pain being endometriosis) but rather the effect of endometriosis (pain).
Undesirable effects How substantial are the undesirable anticipated effects?	Small	The EEWG estimated the undesirable effect of analgesics to be small as the benefits (pain relief) outweigh the risks of analgesics.
Certainty of evidence What is the overall certainty of the evidence of effects?	Very low	The EEWG discussed that the evidence available to the NICE Committee was drawn from a single small crossover RCT of 20 people with endometriosis. The trial was conducted in 1985 and was of very low quality. The direction of the effect for overall pain relief, unintended effects and need for supplementary analgesia outcomes was in favour of analgesics (naproxen sodium) but, due to the small sample size, the study was underpowered and outcome effects had wide confidence intervals. The EEWG discussed the methodological flaws with the trial and agreed with the NICE Committee that the small number of people included in the study and its short duration made it difficult to draw any valid conclusions. The EEWG noted that there is no relevant RCT evidence for the effectiveness of any other types of analgesic for endometriosis-associated pain. The literature search update for the Australian Guideline identified no new studies of analgesics for endometriosis and no studies of analgesics for adenomyosis.
Values Is there important uncertainty about or variability in how much people value the main outcomes?	No important uncertainty or variability	The EEWG acknowledged that systematic study of patients' values and preferences was not undertaken. However, it was agreed that pain relief would be highly valued because pain is a common symptom of endometriosis and, when severe and/or persistent, can be debilitating, affecting a person's ability to perform routine daily activities, greatly limiting lifestyle and quality of life.
Balance of effects Does the balance between desirable and undesirable effects favour the intervention or the comparison?	Probably favours the intervention	The EEWG agreed with the NICE Committee that although there is no good evidence for use of analgesics in management of acute pain specific to endometriosis, there is robust evidence of effectiveness of analgesics for pain management in other areas. The EEWG agreed to give little weight to the limited evidence (in endometriosis) when formulating recommendations, and instead based their decisions on consensus and the experience and expertise of its members. The EEWG extrapolated evidence for effectiveness of analgesia in dysmenorrhoea to inform the consensus recommendation. The EEWG concluded that a short trial of analgesics for first line management of pain in people with endometriosis-associated pain is appropriate. The EEWG agreed with the NICE Committee that as there was no direct evidence on the effectiveness of analgesics in combination with other treatments for endometriosis, and that clinical judgement would be required if considering analgesics in combination with other treatments (e.g. hormonal or surgical treatments). The EEWG agreed that the recommendation for analgesia should be more directive and agreed that NSAIDs (alone or in combination) are preferable to paracetamol alone, based on evidence in people with dysmenorrhoea. The EEWG discussed that it is important to include a time period for a trial of NSAIDs because people should not be expected to continue on suboptimal treatment for a long period of time. The EEWG considered the use of opioids for pain relief and agreed that opioids are out of scope for the Australian Guideline, and the use of opioids is controversial. Although the NICE Committee discussed the World Health Organization (WHO) pain ladder, the EEWG does not support the pain ladder for people with suspected or confirmed endometriosis. Due to the potential for opioid adverse effects and dependency, the EEWG agreed that opioids should only be used in special circumstances but not for chronic non-cancer pain. The EEWG noted that the Australian and New Zealand College of Anaesthesia (ANZCA) Faculty of Pain Medicine have developed recommendations regarding the use of opioid analgesics in patients with chronic non-cancer pain. The EEWG agreed with the NICE

Assessment	EEWG judgement	EEWG considerations
		Committee that a referral would be more appropriate than the addition of an opioid analgesic and that there were other treatment options available.
Acceptability Is the intervention acceptable to key stakeholders?	Yes	The EEWG discussed that use of NSAIDs may be limited in pregnant people with endometriosis-associated pain due to possible adverse effects on the pregnancy (e.g. miscarriage) and the fetus (e.g. malformations). The EEWG noted that there are reports that NSAIDs given to pregnant people cross the placenta and may cause embryo-fetal and neonatal adverse effects, depending on the type of agent, the dose and duration of therapy, the period of gestation, and the time elapsed between maternal NSAID administration and delivery. The EEWG agreed that use of NSAIDs for endometriosis-associated pain is not recommended in pregnancy.
Feasibility Is the intervention feasible to implement?	Yes	The EEWG commented that there are no issues related to feasibility as the interventions (paracetamol, NSAIDs) are all readily available over the counter.
Type of guidance developed by EEWG	Consensus Recommendation and New Consensus Recommendation	**ADAPTED** Consensus Recommendations **#33 & #34** from the Full NICE Guideline. Due to the poor quality and limited evidence, the EEWG based their decisions on consensus and the experience and expertise of its members. The EEWG concluded that a short trial of NSAIDs for first line management of pain in people with endometriosis-associated pain is appropriate and is preferable to paracetamol alone. Two NICE recommendations were adapted and merged to form this recommendation. *Refer to Table App 7 for the wording of NICE recommendations.* **NEW** Consensus Recommendation developed by the EEWG following a review of the evidence on the management of adenomyosis-associated pain (studies published from 2009 onwards).

Q7b – Pharmacological management – Neuromodulators

Table 81 EtD considerations for Q7b – Pharmacological management – Neuromodulators

Assessment	EEWG judgement	EEWG considerations
Problem Is the problem a priority?	Yes	The EEWG agreed that pain management is a high priority problem for people with suspected or confirmed endometriosis and adenomyosis. The EEWG discussed that neuromodulators are used as part of a broader pain management strategy for endometriosis but are not used in the management of adenomyosis-associated pain. Although the NICE Endometriosis Guideline refers to other NICE guidance on neuropathic pain in adults, the EEWG agreed that endometriosis-associated pain is not neuropathic pain and therefore the Australian Guideline should not refer to external guidance for neuropathic pain.
Desirable effects How substantial are the desirable anticipated effects?	Moderate	The EEWG estimated the desirable effect of analgesics to be moderate as neuromodulators aren't targeting the pathology (i.e. the underlying cause of the pain being endometriosis) but rather the effect of endometriosis (pain).
Undesirable effects How substantial are the undesirable anticipated effects?	Moderate	The EEWG estimated the undesirable effects of neuromodulators to be moderate as neuromodulators do not target the underlying cause of the pain (endometriosis) but rather the effect of endometriosis (pain).
Certainty of evidence What is the overall certainty of the evidence of effects?	No included studies	The EEWG discussed that no evidence was identified in the NICE review that addressed the effectiveness of commonly used systemic neuromodulators, and the literature search update conducted for the Australian Guideline identified no new studies. The EEWG agreed with the NICE guideline development Committee that it was disappointing that there was no clinical evidence for the effectiveness of commonly used neuromodulators. The EEWG noted that the two trials identified in the NICE review used local anaesthetics with a procedure called perturbation (which involves the insertion of a thin plastic catheter in the cervical canal). The catheter is then used to infuse the local anaesthetic through the uterine cavity and is then perturbated into the peritoneal cavity. The EEWG agreed with the NICE Committee that the evidence for local anaesthetic (perturbation) in the endometriosis population was of very low to moderate quality, according to GRADE criteria. The EEWG discussed the limitations of the two included studies and had little confidence in their findings.
Values Is there important uncertainty about or variability in how much people value the main outcomes?	No important uncertainty	The EEWG acknowledged that systematic study of patients' values and preferences was not undertaken. However, it was agreed that pain relief would be highly valued because pain is a common symptom of endometriosis and can be debilitating.

Assessment	EEWG judgement	EEWG considerations
Balance of effects Does the balance between desirable and undesirable effects favour the intervention or the comparison?	Does not favour either the intervention or the comparison	The EEWG concluded that there was currently no evidence for the effectiveness of systemic neuromodulators in managing pain of people with endometriosis. The EEWG agreed with the NICE Committee that even though the two identified trials indicated that there might be benefits of the perturbation method for the administration of local anaesthesia, the invasive nature of the procedure raises concerns that the discomfort and possible side effects would outweigh the possible benefits, and that the intervention is unlikely to be used in clinical practice.
Acceptability Is the intervention acceptable to key stakeholders?	Probably yes	
Feasibility Is the intervention feasible to implement?	Probably no	The EEWG agreed with the opinion of the NICE Committee that the nature of perturbation treatment makes it unlikely to be adopted because it would require repeated monthly administrations (to co-occur with the menstrual cycle). The EEWG noted that this is a procedure that is not currently used in the Australia and although it could be implemented, the evidence is not convincing to warrant a change in practice.
Type of guidance developed by EEWG	Consensus Recommendations	**NEW** Consensus Recommendations were developed by the EEWG. Due to the poor quality and limited evidence, the EEWG based their decisions on consensus and the experience and expertise of its members. The EEWG noted that neuromodulators are used as part of a broader pain management strategy. *Refer to Table App 7 for the wording of NICE recommendation.*

Q7c – Pharmacological management – Hormonal medical treatments

Table 82 EtD considerations for Q7c – Pharmacological management – Hormonal medical treatments

Assessment	EEWG judgement	EEWG considerations
Problem Is the problem a priority?	Yes	The EEWG agreed that pain management is a high priority problem for people with suspected or confirmed endometriosis or adenomyosis. The EEWG acknowledged that a large range of hormonal treatment options are available and used in clinical practice. The EEWG discussed that hormonal treatments are now being offered as an alternative to hysterectomy for people with adenomyosis, based on the biological similarity of adenomyosis to endometriosis.
Desirable effects How substantial are the desirable anticipated effects?	Moderate	The EEWG discussed that aside from potential benefits in the management of endometriosis, many hormonal medical treatments will also reduce menstrual bleeding, which some people may consider advantageous. The EEWG also noted that the contraceptive properties of the hormones may be welcome if the person does not wish to become pregnant at that particular point in time.
Undesirable effects How substantial are the undesirable anticipated effects?	Moderate	The EEWG discussed that all hormonal medical treatments have side effects, and the severity and tolerability of the side effects can vary quite significantly. The EEWG also discussed that the contraceptive properties of the hormones may be welcome if the person does not wish to become pregnant at this moment in time, or unwanted if fertility is an issue.

Assessment	EEWG judgement	EEWG considerations
Certainty of evidence What is the overall certainty of the evidence of effects?	Low	The EEWG discussed the evidence identified in the NICE review together with the evidence identified in the literature search update for the Australian Guideline. The EEWG noted that the quality of the evidence used to develop the NICE recommendations on hormonal treatments for pain relief was generally moderate and was drawn from a network meta-analysis (NMA). The EEWG noted comments from the NICE guideline development Committee about the limitations of the available trials but were encouraged that a variety of sensitivity analyses were performed to test assumptions made during modelling and the results seemed robust. The EEWG noted concerns from the NICE Committee that the quality of the evidence was poorer when making recommendations on potential adverse events. The EEWG also noted that the NICE Committee had raised concerns as to the validity of the NMA and its use in decision-making because some of the direct and indirect evidence did not agree. The EEWG also discussed the seven new RCTs of hormonal medical treatments for endometriosis that were identified in the literature search update, one of which compared hormonal medical therapies after surgery. The EEWG discussed the limitations of the studies, noting the short duration of follow-up for many of the studies. The EEWG noted that the new evidence was low quality or very low quality according to GRADE. Risk of bias was serious or very serious in all but one study, which was a treatment not yet TGA-approved (opigolix). The EEWG noted that two RCTs of hormonal medical treatment for adenomyosis were identified in the literature search update, both of which were low quality according to GRADE. The EEWG discussed the limitations of the studies, both of which were small (62 and 68 participants) and had short follow-up.
Values Is there important uncertainty about or variability in how much people value the main outcomes?	Possibly important uncertainty or variability (endometriosis) Important uncertainty or variability (adenomyosis)	The EEWG acknowledged that systematic study of patients' values and preferences was not undertaken and so uncertainty exists about the patient's perspective. The EEWG discussed that the values may differ according to the individual patient preference and other factors such as desired fertility.
Balance of effects Does the balance between desirable and undesirable effects favour the intervention or the comparison?	Don't know (endometriosis) Does not favour either the intervention of the comparison (adenomyosis)	The EEWG agreed with the NICE Committee not to be prescriptive about which treatment path to follow when first line treatment is not effective, not tolerated or is contraindicated and that clinical judgement was required to weigh up the benefits and harms of options that could be used. The EEWG agreed that no specific hormonal treatment can be recommended over another, and treatment should be tailored to the patient in a shared decision-making process. The EEWG agreed that potential adverse events should be discussed with patients alongside the potential benefit for pain relief. The EEWG discussed the duration of time that people should trial hormonal treatment (e.g. 3 months or 6 months) and noted the complexity relating to this. The EEWG agreed to include further advice on the timing of a hormonal treatment trial in implementation materials, particularly to assist GPs. The EEWG acknowledged that although there was very limited evidence available regarding the use of GnRH agonists prior to surgery, they would support the recommendation made by the NICE Committee that preoperative GnRH agonists can reduce surgical complications such as bleeding (based on their experience and knowledge). The decision to use GnRH agonists preoperatively should be made on an individual patient basis and only in severe deep disease. The EEWG noted that the GnRH receptor antagonists examined in the new trials (elagolix and opigolix) were not TGA-approved (at the time of EEWG deliberations) but are likely to be considered by the TGA in the future.
Acceptability Is the intervention acceptable to key stakeholders?	Probably yes	The EEWG agreed that hormonal medical treatments are probably acceptable to people with endometriosis or adenomyosis. The EEWG discussed that some people prefer not to take hormonal treatments while some people prefer to avoid surgery.
Feasibility Is the intervention feasible to implement?	Yes	

Assessment	EEWG judgement	EEWG considerations
Type of guidance developed by EEWG	Evidence-based Recommendations and Consensus Recommendation	**ADAPTED** Evidence-based Recommendation **#36** from the Full NICE Guideline. The EEWG added that hormonal treatment could delay the time to fertility, which may be important depending on the person's age. **ADAPTED** Evidence-based Recommendation **#37** from the Full NICE Guideline. The EEWG clarified in the recommendation that no hormonal treatment is superior to another, and added a footnote to contextualise this recommendation to the Australian healthcare setting. **ADAPTED** Evidence-based Recommendation **#38** from the Full NICE Guideline. The EEWG referred to a 'gynaecologist' rather than a 'gynaecology service, specialist endometriosis service (endometriosis centres) or paediatric and adolescent gynaecology service'. **ADOPTED** Consensus Recommendation **#44** from the Full NICE Guideline. *Refer to Table App 7 for the wording of NICE recommendations.*

Q8 – Alternatives to pharmacological and surgical management

Table 83 EtD considerations for Q8 – Alternatives to pharmacological and surgical management

Assessment	EEWG judgement	EEWG considerations
Problem Is the problem a priority?	Yes	The EEWG agreed that pain management is a high priority problem for people with suspected or confirmed endometriosis or adenomyosis. The EEWG discussed that treatment, for many people, will involve a combination of therapies given over their lifetime depending on their circumstances at any given time. Although some text in the NICE Guideline implied that people may seek alternatives to pharmacological and surgical management after exhausting all other options, the EEWG noted that this is not always the case, acknowledging that some people may choose complementary and alternative therapies as an adjunct to medical and surgical management. The evidence review was intentionally broad to look for evidence on a wide range of interventions covering behavioural/psychological medicine, lifestyle medicine, physical methods and other interventions (including dietary supplements, herbal medicine, homeopathy, etc).
Desirable effects How substantial are the desirable anticipated effects?	Varies	The EEWG discussed that the desirable effects could be large for behaviour medicine but small for some of the other interventions.
Undesirable effects How substantial are the undesirable anticipated effects?	Varies	The EEWG discussed that there are a large number of alternatives to pharmacological and surgical management, and the risk of harms varies across the interventions.

Assessment	EEWG judgement	EEWG considerations
Certainty of evidence What is the overall certainty of the evidence of effects?	Moderate	The EEWG discussed the evidence identified in the NICE review together with the evidence identified in the literature search update for the Australian Guideline. The NICE review identified 10 RCTs, mainly looking at different forms of acupuncture or Chinese herbal medicine (CHM). The NICE guideline development Committee noted that although there is some evidence that CHM may be effective, they expressed their concern regarding standardisation, regulation, efficacy and safety of these medicines. The EEWG discussed that ultimately, the NICE Committee took only one study through the GRADE process because they were of the opinion that the evidence was very uncertain and of limited value. The one study that was appraised by the NICE Committee using GRADE compared acupuncture with sham acupuncture in 42 patients and was judged to be moderate quality. The EEWG discussed the reliability of sham acupuncture, noting that some types of acupuncture would be impossible to sham (e.g. electroacupuncture). The EEWG discussed the findings of the study and was not convinced that there was much difference between study arms (other than at 6 months). The EEWG noted that the literature search update identified 7 new studies of alternatives to pharmacological and surgical management in people with endometriosis but no studies in people with adenomyosis. The EEWG discussed the strengths and weaknesses of each study and agreed that only two of the new studies were potentially worthy of further consideration and should be appraised using GRADE. The first was a small study from Brazil that compared melatonin with placebo for the treatment of pain in 40 people with endometriosis confirmed by laparoscopic surgery. The EEWG noted that the study was judged to have no serious risk of bias, but the dose of melatonin was high (five times the dose recommended by the TGA for insomnia) and adverse events were not captured as a study outcome. The body of evidence for melatonin was low certainty using the GRADE approach, with downgrading due to serious indirectness (higher dose than is used in Australia) and serious imprecision (wide confidence intervals likely due to the small sample size). The EEWG discussed that there are reports that melatonin is effective for pain relief for other conditions, but the mechanism of action is unknown for endometriosis-associated pain. The EEWG commented that the improvement in pain seen in the study may have been due to improvement in sleep, and that melatonin is reasonably well tolerated compared with other medications to improve sleep. The other study that was of interest to the EEWG compared palmitoylethanolamine (PEA)-transpolydatin with placebo or celecoxib in people who have had first-line laparoscopic conservative surgery. The Italian study was small and judged to be at high risk of bias. The EEWG commented that the laparoscopic surgical procedure could have contributed to the reduction in pelvic pain, and there are potential harms of PEA-transpolydatin. The EEWG agreed that although naturopaths are recommending PEA, the available evidence does not support the use of this intervention for endometriosis-associated pain.
Values Is there important uncertainty about or variability in how much people value the main outcomes?	No important uncertainty or variability	The EEWG acknowledged that systematic study of patients' values and preferences was not undertaken. However, it was agreed that pain relief would be highly valued because pain is a common symptom of endometriosis and can be debilitating.
Balance of effects Does the balance between desirable and undesirable effects favour the intervention or the comparison?	Varies	The EEWG noted concerns raised by the NICE Committee that many of the currently used alternatives to pharmacological and surgical management were not supported by evidence. The EEWG agreed with the NICE Committee that the lack of evidence specifically addressing a population of people with endometriosis (and adenomyosis) made it difficult to draft recommendations for these management strategies, particularly for dietary interventions. The EEWG noted that some of the NICE Committee members, based on their experience, suggested that physiotherapy and psychological pain management approaches are definitely effective. While some members of the EEWG concurred with these comments and noted that physiotherapy is a well-established intervention for pain relief, it was agreed that evidence for these approaches is lacking in people with endometriosis or adenomyosis. The EEWG discussed whether the Australian Guideline could include a comment on the effectiveness of physiotherapy based on research on other pain populations, but agreed that the guideline would need to make it clear that there is no evidence specifically in people with endometriosis- or adenomyosis-associated pain. Some members of the EEWG commented that people with endometriosis-associated pain should not be discouraged from trying alternative treatment options but should be cautioned on particular diets and herbal medicine due to uncertainty about interactions and concerns regarding side-effects and lack of supporting evidence. The EEWG discussed that there is a very real risk of harm from Chinese herbal medicine, but the trials do not often report adverse events.

Assessment	EEWG judgement	EEWG considerations
		The EEWG discussed that people with endometriosis often ask about acupuncture as a treatment option. The EEWG agreed that evidence for the effectiveness of acupuncture for endometriosis-associated pain is limited and there is an out of pocket expense to patients. The EEWG acknowledged that acupuncture can have negative side effects, although the harms are not as concerning as Chinese herbal medicine. Overall, the EEWG agreed that alternative treatment options could be considered as complementary to pharmacological and surgical management, but not in place of pharmacological and surgical management. The EEWG discussed fertility considerations and expressed concern that data on side effects of complementary and alternative therapies in pregnant people are limited.
Acceptability Is the intervention acceptable to key stakeholders?	Varies	The EEWG discussed that cost is a major consideration for people with endometriosis, who already have a significant financial burden. Complementary and alternative therapies are generally not covered by Medicare.
Feasibility Is the intervention feasible to implement?	Don't know	The EEWG agreed that acceptability and feasibility would be patient driven and that patient expense and out of pocket costs are important factors. The EEWG discussed that melatonin is not approved for pain relief in Australia and is not readily available. The EEWG also noted that PEA is only available from compounding pharmacies.
Type of guidance developed by EEWG	Evidence-based Recommendations and Consensus Recommendation	**ADAPTED** Evidence-based Recommendation **#39** from the Full NICE Guideline. The EEWG acknowledged the potential harms associated with the use of Chinese herbal medicines or supplements based on the evidence that was reviewed. *Refer to Table App 8 for the wording of NICE recommendation.* **NEW** Evidence-based Recommendation developed by the EEWG following a review of the evidence on acupuncture for the management of endometriosis-associated pain. **NEW** Consensus Recommendation developed by the EEWG following a review of the evidence on alternatives to pharmacological and surgical management for the management of adenomyosis-associated pain (studies published from 2009 onwards).

Q9a – Surgical management

Table 84 EtD considerations for Q9a – Surgical management – Ablation or excision

Assessment	EEWG judgement	EEWG considerations
Problem Is the problem a priority?	Yes	The EEWG agreed with the NICE guideline development Committee that surgical treatment is an important part of the management of endometriosis, aiming to remove or destroy endometriotic deposits and divide adhesions with restoration of normal anatomy. Surgical treatments can be performed by laparoscopy (traditional or robotic) or as an open procedure (laparotomy). The EEWG discussed that endometriotic deposits can be treated by excision or ablation and that surgical techniques may be influenced by the surgeons' training and preferences.
Desirable effects How substantial are the desirable anticipated effects?	Moderate	The EEWG agreed that the beneficial effects of surgery are large. The EEWG discussed that in addition to pain relief, surgery has a role in the management of recurrent disease, although it is recognised that outcomes may reduce with increasing numbers of operations.
Undesirable effects How substantial are the undesirable anticipated effects?	Moderate	The EEWG discussed that there are harms related to surgery.
Certainty of evidence What is the overall certainty of the evidence of effects?	Very low	The EEWG discussed the evidence identified in the NICE review together with the evidence identified in the literature search update for the Australian Guideline. For comparison between different surgical techniques, the EEWG noted that the quality of the evidence was very low for surgical management of endometriosis and absent for surgical management of adenomyosis. The EEWG agreed with the NICE Committee about the difficulty of conducting high quality randomised studies, particularly as randomising patients to either excisional or ablative laparoscopic treatment can be impractical, especially where there is deep endometriosis affecting bowel, bladder and ureter. The EEWG noted that the literature search update identified no new trials comparing surgery with diagnostic laparoscopy but identified one new trial comparing robotic laparoscopic ablation with robotic laparoscopic excision for superficial endometriosis-associated pain. This new trial was small and the evidence was very low quality according to GRADE. The EEWG discussed the

Assessment	EEWG judgement	EEWG considerations
		limitations of the trial, noting the high rate of dropouts (over 40% at 6 months) and that the beneficial effect was statistically significant but not necessarily clinically significant. The EEWG agreed to place little weight on this new trial given that robotic surgery is not commonly used in Australia for endometriosis. The EEWG noted the comment from the NICE Committee that the current literature does not provide a clear answer because the stage of endometriosis is often not sufficiently clearly defined in research studies, and the treatment modalities used are multiple and varied. The EEWG agreed that larger studies with long-term follow-up of patient-centred outcomes are required.
Values Is there important uncertainty about or variability in how much people value the main outcomes?	Important uncertainty or variability	The EEWG acknowledged that systematic study of patients' values and preferences was not undertaken and so uncertainty exists about the patient's perspective. The EEWG agreed that fertility may be a strongly influencing factor in treatment choices for many people.
Balance of effects Does the balance between desirable and undesirable effects favour the intervention or the comparison?	Does not favour either the intervention or the comparison	The EEWG discussed that diagnostic laparoscopy is a valuable tool that provides the most accurate diagnosis and also provides the opportunity to treat. The EEWG agreed with the NICE Committee that excisional treatment be recommended over ablative treatment as the evidence showed that there was lower risk of recurrence of endometrioma and the GDC suggested that ablative surgery had a greater negative impact on ovarian reserve. The EEWG discussed that severe endometriosis involving the bowel, bladder and ureter may require additional surgical expertise, including colorectal surgeons and urologists. The EEWG acknowledged that there is no evidence for or against excisional or ablative surgery in the treatment of adenomyosis. The EEWG discussed that surgical options are limited for the treatment of adenomyosis if fertility is to be preserved.
Acceptability Is the intervention acceptable to key stakeholders?	Varies	
Feasibility Is the intervention feasible to implement?	Yes	The EEWG discussed that laparoscopic treatment (with or without subsequent hormonal treatment) is the 'gold-standard' for treating endometriosis.
Type of guidance developed by EEWG	Evidence-based Recommendations and Consensus Recommendation and Committee Opinion	**OMITTED** Evidence-based Recommendation **#40** from the Full NICE Guideline because a similar version of the recommendation is captured under Q6 (staging systems). **ADOPTED** Evidence-based Recommendation **#41** from the Full NICE Guideline. **ADOPTED** Evidence-based Recommendation **#42** from the Full NICE Guideline. **ADAPTED** Evidence-based Recommendation **#45** from the Full NICE Guideline. The EEWG added 'previous ovarian surgery' as something to take into account, and removed reference to the NICE guideline on fertility problems as this was not thought to be relevant to the Australian context. *Refer to Table App 9 for the wording of NICE recommendation.* **NEW** Committee Opinion developed by the EEWG to acknowledge that deeply invasive endometriosis should be referred to a clinician with appropriate skills. **NEW** Consensus Recommendation developed by the EEWG. The EEWG agreed that it was important to specifically acknowledge that no trials were identified relating to surgical management of adenomyosis.

Q9b – Combination of surgery and hormonal treatment

Table 85 EtD considerations for Q9b – Combination of surgery and hormonal treatment

Assessment	EEWG judgement	EEWG considerations
Problem Is the problem a priority?	Yes (endometriosis) Probably yes (adenomyosis)	The EEWG discussed that reduction of pain due to presumed recurrence currently involves the use of hormonal treatments pre- or post-surgery. The rationale for this, which is noted in the NICE Guideline, is that hormonal treatments reduce circulating levels of oestrogen leading to lighter or no periods, theoretically causing shrinkage of existing endometriosis lesions and preventing new lesions developing. The EEWG discussed that although adenomyosis and endometriosis are different diseases, both grow and regress in an oestrogen-dependent fashion. However, surgical options are not as useful for adenomyosis.

Assessment	EEWG judgement	EEWG considerations
Desirable effects How substantial are the desirable anticipated effects?	Varies (endometriosis) Don't know (adenomyosis)	The EEWG agreed that in general, combination hormonal and surgical treatment is anticipated to have a desirable effect on the pain relief in people with endometriosis, but there are many options available.
Undesirable effects How substantial are the undesirable anticipated effects?	Varies (endometriosis) Don't know (adenomyosis)	
Certainty of evidence What is the overall certainty of the evidence of effects?	Low (endometriosis) No included studies (adenomyosis)	The EEWG discussed the evidence identified in the NICE review together with the evidence identified in the literature search update for the Australian Guideline. The EEWG noted that all 12 trials included in the NICE review compared pharmacological therapy after surgery versus placebo or no pharmacological therapy after surgery. The EEWG discussed the quality of the evidence included in the NICE review, which ranged from moderate to very low. The EEWG noted that the descriptions of the surgery performed were poor and that the included studies had been published over a 30-year period. Over this time, the techniques used had not changed greatly but there had been significant improvement in laparoscopic technology resulting in a surgeon's ability to remove more diseased tissue through improved visualisation. The EEWG agreed with the NICE Committee that it is difficult to draw overall conclusions from the included studies regarding the quality of the surgery performed, and that this might also affect assessment of the effectiveness of the additional hormonal suppression therapy as people might have a comparatively greater treatment effect where less diseased tissue had been removed by surgery. The EEWG discussed the three new trials identified in the literature search update, all of which compared pharmacological therapy after surgery versus placebo or no pharmacological therapy after surgery. The three trials were from Thailand, China and Northern Taiwan and all were small and judged to have serious or very serious risk of bias. The EEWG discussed the limitations of these trials and agreed that the evidence was of low or very low certainty according to GRADE.
Values Is there important uncertainty about or variability in how much people value the main outcomes?	No important uncertainty or variability (endometriosis)	
Balance of effects Does the balance between desirable and undesirable effects favour the intervention or the comparison?	Probably favours the intervention (endometriosis) Don't know (adenomyosis)	The EEWG noted that the NICE Committee based their recommendations on the findings of the NMA, which demonstrated that adding hormonal treatment <u>following</u> surgery (laparoscopic excision or ablation) reduces the risk of recurrence and symptoms, so it should be offered to people post-surgery unless they want to conceive. The EEWG noted comments from the NICE Committee that hormonal treatment <u>prior</u> to surgery would only be suitable for people with deep endometriosis involving the bowel, bladder or ureter. The NICE Committee noted that this would usually lead to less bleeding and would therefore aid the surgical procedure. The EEWG noted the lack of evidence in adenomyosis populations and discussed that adenomyosis is a condition that is usually treated with either hormonal therapy or surgery (e.g. adenomyectomy or hysterectomy) rather than combined therapies. The EEWG agreed that hormonal therapy may be an offered as a first line treatment for adenomyosis, depending upon patient preference and clinical judgement.
Acceptability Is the intervention acceptable to key stakeholders?	Yes (endometriosis) Probably yes (adenomyosis)	
Feasibility Is the intervention feasible to implement?	Yes (endometriosis) Yes (adenomyosis)	
Type of guidance developed by EEWG	Evidence-based Recommendation and Consensus Recommendation	**ADAPTED** Evidence-based Recommendation **#46** from the Full NICE Guideline. The EEWG added that the chosen therapy should consider patient preferences, and removed the footnote as this was not thought to be relevant to the Australian context. *Refer to Table App 9 for the wording of NICE recommendation.* **NEW** Consensus Recommendation developed by the EEWG following a review of the evidence on combination surgery plus hormonal treatment for adenomyosis.

Q9c – Hysterectomy

Table 86 EtD considerations for Q9c – Hysterectomy

Assessment	EEWG judgement	EEWG considerations
Problem Is the problem a priority?	Yes	The EEWG agreed with the NICE guideline development Committee that endometriosis by definition is endometriotic tissue outside the uterus, which means that it is not expected to be cured by hysterectomy. The EEWG discussed that hysterectomy combined with surgical excision/ablation of endometriosis is currently offered for the treatment of endometriosis when medical and hysterectomy sparing surgical options have been offered, failed or are inappropriate. Hysterectomy is not currently offered for the treatment of asymptomatic endometriosis.
Desirable effects How substantial are the desirable anticipated effects?	Varies	The EEWG agreed that the size of the benefit varies. For pain relief alone, the anticipated effect would be small but for dysmenorrhoea the benefit may be large. The EEWG discussed that hysterectomy (with removal of the endometriotic lesions at the same time) may be particularly beneficial for people with adenomyosis or heavy menstrual bleeding not responding to other treatments.
Undesirable effects How substantial are the undesirable anticipated effects?	Varies	The EEWG discussed that hysterectomy is associated with potential morbidity and a very low risk of mortality. People who have a hysterectomy are no longer be able to have children. There are also risks associated with early oophorectomy (e.g. osteoporosis, cardiovascular disease). The EEWG also acknowledged the adverse effects of a surgical menopause, the need for hormone replacement until the age of natural menopause, and the potential for recurrence of the disease.
Certainty of evidence What is the overall certainty of the evidence of effects?	Very low	The EEWG discussed the evidence identified in the NICE review together with the evidence identified in the literature search update for the Australian Guideline. The NICE review identified only 2 retrospective cohort studies that compared hysterectomy only and hysterectomy plus oophorectomy. The evidence was of very low quality due to risk of bias in both studies (study design, outcome selection and detection bias), imprecision of results in 1 study (large confidence interval) and indirectness in 1 study (age of study limiting applicability for modern surgical techniques). The EEWG noted the concerns raised by the NICE Committee that although these studies reported a clinical benefit, the findings are uncertain due to limitations in study design and the ability to be applied to the current population. The literature search update identified only one new study, which was a retrospective before-and-after study in 16 people with debilitating symptoms of endometriosis who underwent hysterectomy with bilateral salpingo-oophorectomy. This study provided very low quality evidence for improvement in health-related quality of life.
Values Is there important uncertainty about or variability in how much people value the main outcomes?	Important uncertainty or variability	The EEWG acknowledged that systematic study of patients' values and preferences was not undertaken and so uncertainty exists about the patient's perspective. The EEWG discussed important variability in values depending on disease presentation (endometriosis, adenomyosis or both).
Balance of effects Does the balance between desirable and undesirable effects favour the intervention or the comparison?	Varies	The EEWG expressed concern about the lack of evidence in this area and commented that they had expected to find studies of hysterectomy for adenomyosis. The EEWG acknowledged that only very general guidance could be made and that it would be driven by expert opinion rather than evidence. The EEWG agreed that there are some indications for hysterectomy but also acknowledged that there can be significant social / psychological effects of hysterectomy. The EEWG discussed the complexity and spectral nature of the disease, noting that decisions for or against hysterectomy would be dependent on patient preference (informed choice is very important) and pathology. The EEWG agreed that the recommendation for adenomyosis should acknowledge that there is no evidence that hysterectomy resolves adenomyosis-associated pain, but it will resolve heavy menstrual bleeding.
Acceptability Is the intervention acceptable to key stakeholders?	Varies	The EEWG discussed that people with endometriosis are a heterogeneous group and the acceptability of hysterectomy varies depending on recurrence, extent of disease, personal situation, etc.
Feasibility Is the intervention feasible to implement?	Yes	

Assessment	EEWG judgement	EEWG considerations
Type of guidance developed by EEWG	Evidence-based Recommendation and Consensus Recommendations	**ADAPTED** Consensus Recommendation **#47** from the Full NICE Guideline. The EEWG added that there is no evidence for or against the effectiveness of hysterectomy for endometriosis. **ADOPTED** Evidence-based Recommendation **#48** from the Full NICE Guideline. **ADAPTED** Consensus Recommendation **#49** from the Full NICE Guideline. The EEWG removed the link to the NICE guideline on menopause. The EEWG also duplicated the recommendation for adenomyosis. *Refer to Table App 9 for the wording of NICE recommendations.* **NEW** Consensus Recommendation developed by the EEWG following a review of the evidence on hysterectomy for the treatment of adenomyosis.

Q10 – Management strategies to enhance fertility

Table 87 EtD considerations for Q10 – Management strategies to enhance fertility

Assessment	EEWG judgement	EEWG considerations
Problem Is the problem a priority?	Yes	The EEWG discussed that endometriosis is recognised as an important cause of infertility, and that management of endometriosis, as well as fertility interventions, aim to improve a person's chances of pregnancy. The EEWG discussed that even in those people where fertility is not a direct intended effect, fertility is always discussed.
Desirable effects How substantial are the desirable anticipated effects?	Large	The EEWG discussed that the capacity to maintain reproductive function has a large impact.
Undesirable effects How substantial are the undesirable anticipated effects?	Trivial	
Certainty of evidence What is the overall certainty of the evidence of effects?	Moderate	The EEWG noted that no new studies were identified in the literature search update for the Australian Guideline and discussed the evidence identified in the NICE review. The network meta-analysis (NMA) in the NICE review examined evidence on rates of spontaneous pregnancy and contained 16 trials of 11 treatment classes. The EEWG noted that 7 studies were at high risk of bias, 7 were at moderate risk of bias and 2 studies were at low risk of bias. GRADE criteria are currently not applied to NMA evidence, but – based on study quality – the body of the evidence would be no better than moderate quality. The EEWG noted the results of the NMA, which showed that laparoscopic surgical management of endometriosis was found to lead to significantly more spontaneous pregnancies than diagnostic laparoscopy, while danazol/gestrinone led to fewer spontaneous pregnancies than placebo. For all other treatments there was considerable uncertainty regarding their effect on spontaneous pregnancy.
Values Is there important uncertainty about or variability in how much people value the main outcomes?		The EEWG acknowledged that systematic study of patients' values and preferences was not undertaken.
Balance of effects Does the balance between desirable and undesirable effects favour the intervention or the comparison?	Varies	The EEWG noted that the focus in the NICE review on spontaneous pregnancy as an outcome has limitations in that it excludes any assistive reproductive management. The EEWG noted the comments from the NICE guideline development Committee that studies in the NMA tended to include people with either minimal or mild endometriosis (AFS stage 1–2) or moderate or severe endometriosis (AFS stage 3–4), but there were insufficient data available to investigate fertility outcomes by severity of endometriosis. The EEWG agreed with the conclusions of the NICE Committee that there was evidence to support the use of surgery in people with milder endometriosis to improve fertility; however, the evidence was less clear regarding fertility outcomes for people with moderate to severe endometriosis and the NICE Committee noted there are adverse effects, including endometrioma and peritonitis after egg collection, in this group. The EEWG agreed that surgery should be discussed as a treatment option in conjunction with a fertility expert who would then be able to assess the ovarian reserve prior to surgery. The EEWG noted the evidence showing lower spontaneous pregnancy rates (not rates following assisted conception) in all people with endometriosis on hormonal suppression treatments regardless of the severity of their condition. The EEWG therefore agreed with the NICE Committee that hormonal suppression treatment should not be offered postoperatively if fertility was the priority.

Assessment	EEWG judgement	EEWG considerations
Acceptability Is the intervention acceptable to key stakeholders?	Varies	
Feasibility Is the intervention feasible to implement?	Yes	
Type of guidance developed by EEWG	Evidence-based Recommendations and Committee Opinion	**ADAPTED** text under Section 12.3.4 from the Full NICE Guideline to acknowledge that management of endometriosis-associated infertility should involve an interdisciplinary (not multidisciplinary) team. The EEWG designated this a Committee Opinion. **ADAPTED** Evidence-based Recommendation **#52** from the Full NICE Guideline. The EEWG removed reference to the NICE guideline on fertility problems. **ADAPTED** Evidence-based Recommendations **#50 & #51** from the Full NICE Guideline. The EEWG merged the two NICE recommendations so that one recommendation contains guidance relating to endometriosis and endometriomas. **ADAPTED** Evidence-based Recommendation **#53** from the Full NICE Guideline. The EEWG referred to hormonal 'suppression' treatments to add clarity on the type of hormonal treatment. *Refer to Table App 10 for the wording of NICE recommendations.*

Q11 – Follow-up in people who are asymptomatic

Table 88 EtD considerations for Q11 – Follow-up in people who are asymptomatic

Assessment	EEWG judgement	EEWG considerations
Problem Is the problem a priority?	Don't know	The EEWG agreed that the need for follow-up (prophylactic surgery, second-look surgery, repeat ultrasound) is unclear due to lack of data.
Desirable effects How substantial are the desirable anticipated effects?		
Undesirable effects How substantial are the undesirable anticipated effects?		The EEWG discussed the potential harms of follow-up interventions in people who are symptomatic, including fertility issues and general risks of surgery.
Certainty of evidence What is the overall certainty of the evidence of effects?	No included studies	The EEWG noted that no evidence was identified that met the eligibility criteria.
Values Is there important uncertainty about or variability in how much people value the main outcomes?		The EEWG acknowledged that systematic study of patients' values and preferences was not undertaken and so uncertainty exists about the patient's perspective.
Balance of effects Does the balance between desirable and undesirable effects favour the intervention or the comparison?		The EEWG agreed with the NICE recommendation to consider follow-up (with or without examination and pelvic imaging) in asymptomatic people with deep endometriosis involving the bowel, bladder or ureter, or people who have an endometrioma larger than 3 cm.
Acceptability Is the intervention acceptable to key stakeholders?		
Feasibility Is the intervention feasible to implement?		
Type of guidance developed by EEWG	Consensus Recommendation	**ADAPTED** Consensus Recommendation **#12** from the Full NICE Guideline. The EEWG clarified that the recommendation refers to asymptomatic people. *Refer to Table App 4 for the wording of NICE recommendation.*

Q12 – Secondary prevention of endometriosis

Table 89 EtD considerations for Q12 – Secondary prevention of endometriosis

Assessment	EEWG judgement	EEWG considerations
Problem Is the problem a priority?	Yes	The EEWG agreed with the NICE guideline development Committee that in light of the high rate of recurrence of endometriosis, affecting long-term quality of life for many people, improvement in long-term control of the condition is clinically very important. The EEWG also discussed the high rate of reoperation for endometriosis with associated risks of surgery and considered that avoidance of repeat surgery by the use of long -term medical therapy would be beneficial. Reduction of pain due to presumed recurrence currently involves the use of hormonal treatments pre- or post-surgery. The rationale is that hormonal treatments reduce circulating levels of oestrogen leading to lighter or no periods, theoretically causing shrinkage of existing endometriosis lesions and preventing new lesions developing. The EEWG also discussed that prophylactic surgery is sometimes undertaken as a secondary prevention measure.
Desirable effects How substantial are the desirable anticipated effects?	Moderate	The EEWG discussed that there are many hormonal treatment options available, and the size of the benefit will also depend on how the treatments are administered and the stage of disease.
Undesirable effects How substantial are the undesirable anticipated effects?	Varies	The EEWG acknowledged there are known side effects with hormonal treatments that some people may wish to avoid. There are also potential harms associated with prophylactic surgery.
Certainty of evidence What is the overall certainty of the evidence of effects?	Very low	The EEWG discussed the evidence identified in the NICE review together with the evidence identified in the literature search update for the Australian Guideline. All evidence was very low quality according to GRADE and the duration of follow-up in most studies was insufficient. The EEWG noted that the available evidence in the NICE review showed no clinically significant difference between hormonal treatment and no treatment after surgery for recurrence of endometriosis at 12 or 24 months. Although hormonal treatment appeared to have a clinically significant beneficial effect on endometrioma recurrence at 13-36 months, there was no difference between hormonal treatment and no treatment after surgery at 5 years. The EEWG discussed the limitations in the new studies identified in the literature search update and agreed that the evidence is not reliable; one study that showed no beneficial impact of postoperative LNG-IUS included a GnRH agonist in both arms for 6 months so the results were confounded, and the other study found a statistically significant benefit of postoperative GnRH agonist but was poorly reported so there was lack of clarity around the definition of recurrence.
Values Is there important uncertainty about or variability in how much people value the main outcomes?	Probably no important uncertainty or variability	The EEWG acknowledged that systematic study of patients' values and preferences was not undertaken. However, improvement in long-term control of the condition was clinically very important.
Balance of effects Does the balance between desirable and undesirable effects favour the intervention or the comparison?		The EEWG noted that the NICE Committee had commented that their network meta-analysis demonstrated that adding hormonal treatment following surgery (laparoscopic excision or ablation) reduces the risk of recurrence and symptoms, so it should be offered to people post-surgery unless they want to conceive. The EEWG noted the lack of evidence and potential for surgical complications with prophylactic surgery and agreed that it should not be recommended in the absence of symptoms.
Acceptability Is the intervention acceptable to key stakeholders?	Yes	
Feasibility Is the intervention feasible to implement?		
Type of guidance developed by EEWG	Consensus Recommendation	**NEW** Consensus Recommendation developed by the EEWG following a review of the evidence on treatments for prevention of recurrence (no evidence available for prophylactic surgery).

Appendix A Summary of NICE 2017 endometriosis guideline questions and recommendations

The tables below show each review question addressed in the **NICE 2017 Guideline**, together with the ensuing clinical evidence statements and recommendations.

The Full NICE 2017 Guideline also contains clinical Evidence Profile Tables and Evidence-to-Decision summaries, which provides further context for the decision-making leading to the formulation of recommendations. The findings of *de novo* economic analyses were also factored into decision-making for NICE and are included in the Full Guideline.

Organisation of care

Table App 1 NICE 2017 Guideline evidence statements and recommendations: Organisation of care

Content	Description
Specialist services	
Review question	What is the clinical and cost effectiveness of specialist endometriosis services?
Interventions in scope	Specialist services (colorectal surgeon, urologist, pain management specialist, sub-fertility specialist, specialist endometriosis nurse, gynaecologist specialising in laparoscopic surgery, specialist nurses in gynaecology or fertility) Gynaecology services (mild to moderate endometriosis) Specialist endometriosis centre (severe endometriosis)
Critical outcomes	Pain, QoL, effect on daily activities
GRADE rating	No clinical evidence identified
Clinical evidence statements	*Not applicable.* *"Due to the lack of applicable clinical evidence, the Committee based the recommendations on the health economic model as well as on their experience and expertise. They considered that it would be possible to stratify women with endometriosis involving the bowel, bladder or ureter to specialist endometriosis services (endometriosis centres) and that this is therefore a targeted smaller group of women that would receive this service."*
Recommendations	**1.** Set up a managed clinical network for women with suspected or confirmed endometriosis, consisting of community services (including GPs, practice nurses, school nurses and sexual health services), gynaecology services and specialist endometriosis services (endometriosis centres). **2.** Gynaecology services for women with suspected or confirmed endometriosis should have access to: • a gynaecologist with expertise in diagnosing and managing endometriosis, including training and skills in laparoscopic surgery • a gynaecology specialist nurse with expertise in endometriosis • a multidisciplinary pain management service • a healthcare professional with an interest in gynaecological imaging • fertility services. **3.** Specialist endometriosis services (endometriosis centres) should have access to: • gynaecologists with expertise in diagnosing and managing endometriosis, including advanced laparoscopic surgical skills • a colorectal surgeon with an interest in endometriosis • a urologist with an interest in endometriosis • an endometriosis specialist nurse • a multidisciplinary pain management service with expertise in pelvic pain • a healthcare professional with specialist expertise in gynaecological imaging of endometriosis • advanced diagnostic facilities (for example, radiology and histopathology) • fertility services.
Timing	
Review question	Is there an association between duration of symptoms before laparoscopy and /or treatment and treatment outcomes?
Interventions in scope	Duration of symptoms followed by early laparoscopy and treatment
Critical outcomes	Pain, QoL, effect on daily activities
GRADE rating	No clinical evidence identified

Content	Description
Clinical evidence statements	*Not applicable.* *The Committee agreed with the conclusions from the de novo health economic model which showed that in all patient populations with endometriosis, a delay in diagnosis and treatment was not beneficial to the NHS given their typical willingness to trade resources for health at around £20,000. The model demonstrated that delays in treatment led to an overall cost saving despite the increased cost of treating more progressed endometriosis, but found that this saving was outweighed by the harm to the quality of life of the women with endometriosis that a delay caused. In the absence of clinical evidence the conclusion from the de novo economic model is consistent with clinical expert consensus.*
Recommendations	**4.** Community, gynaecology and specialist endometriosis services (endometriosis centres) should: • provide coordinated care for women with suspected or confirmed endometriosis • have processes in place for prompt diagnosis and treatment of endometriosis, because delays can affect quality of life and result in disease progression.

Abbreviations: GP, general practitioner; NICE, National Institute of Health Care Excellence; NHS, National Health Service; QoL, quality of life.

Information and support

Table App 2 NICE 2017 Guideline evidence statements and recommendations: Information and support

Content	Description
Review question	What information and support do women with endometriosis and their families find helpful and what are the barriers and facilitators in the provision of these information and support needs?
Interventions in scope	Support groups; volunteer supporters; Helplines Methods of information provision (Tools to facilitate): verbal, written, online (and online networks), apps; in groups (peer groups) online or face or face to face, 1:1 advocacy support, online health forum
Critical outcomes	HRQoL, psychological wellbeing, participant satisfaction
GRADE rating	*No quantitative studies were identified – GRADE not used.* *17 qualitative studies were assessed as having low to moderate risk of bias*
Clinical evidence statements	*"A number of themes emerged from the semi-structured interviews, interviews, focus groups and support groups of women with endometriosis and also their partners. The central theme of information content with subthemes of information type, social, healthcare professional, diagnosis, condition and psychological information are interlinked and have been perceived as important and helpful or as barriers by women with endometriosis and their partners and families."*
Recommendations	**13.** Be aware that endometriosis can be a long-term condition, and can have a significant physical, sexual, psychological and social impact. Women may have complex needs and require long-term support. **14.** Assess the individual information and support needs of women with suspected or confirmed endometriosis, taking into account their circumstances, symptoms, priorities, desire for fertility, aspects of daily living, work and study, cultural background, and their physical, psychosexual and emotional needs. **15.** Provide information and support for women with suspected or confirmed endometriosis, which should include: • what endometriosis is • endometriosis symptoms and signs • how endometriosis is diagnosed • treatment options • local support groups, online forums and national charities, and how to access them. **16.** If women agree, involve their partner (and/or other family members or people important to them) and include them in discussions. For more guidance on providing information to people and involving family members and carers, see the NICE guideline on patient experience in adult NHS services.

Abbreviations: HRQoL, health-related quality of life; NICE, National Institute of Health Care Excellence.

Signs and symptoms

Table App 3 NICE 2017 Guideline evidence statements and recommendations: Signs and symptoms

Content	Description
Review question	What are the symptoms and signs of endometriosis?
Signs & symptoms to be considered	Signs Vaginal (visible endometriosis, severe vaginismus); pelvic (palpable nodules in rectovaginal septum and uterosacral ligaments, fixed or tethered uterus and pelvic mass, tender adnexa, tenderness); rectal (palpable extrinsic pelvic mass); renal (loin tenderness, palpable mass); family history of endometriosis Symptoms Pelvic symptoms (pelvic pain, cyclical/non-cyclical); uterus pain (dysmenorrhoea and abnormal bleeding (prolonged and heavy and inter-menstrual bleeding); bowel (rectal bleeding, dyschezia, bloating, constipation and diarrhoea); bladder (bladder pain or irritability, blood in the urine); vaginal pain (painful sex (dyspareunia), pain when using tampons); referred pain (back, leg, thigh, hip); infertility; fatigue; psychological effects (isolation, depression/anxiety, low self-esteem, low mood, poor body image, loss of libido)
Critical outcomes	Confirmed diagnosis of endometriosis at follow-up; severity of endometriosis; referral to diagnostic services
GRADE rating	*Prognostic question – GRADE not used. 3 identified studies were assessed as having moderate risk of bias*
Clinical evidence statements	Pelvic pain Evidence from 1 study (n=1079, **moderate risk of bias**) showed there was a significantly increased risk of stage III/IV endometriosis in women who had symptoms of chronic pelvic pain. Evidence from 1 study (n=495, **moderate risk of bias**) showed there was no increased risk of endometriosis in women who had pelvic pain. Dysmenorrhoea Evidence from 1 study (n=1079, **moderate risk of bias**) showed there was no increased risk of endometriosis in women who had symptoms of mild dysmenorrhoea; however, moderate quality evidence from 1 study (n=429) showed a significantly increased risk of endometriosis in women with increasing severity of dysmenorrhoea. Evidence from 2 studies (**moderate risk of bias**) showed that there was a significantly increased risk of stage III/IV endometriosis in women who had dysmenorrhoea of any type (n=495 and n=1079) as well as moderate, severe or recently intensified dysmenorrhoea (n=1079). Irregular cycle Evidence from 1 study (n=1079, **moderate risk of bias**) showed there was no increased risk of any type or stage III/IV endometriosis in women who had an irregular cycle. Infertility history Evidence from 2 studies (n=495 and n=429, **moderate risk of bias**) showed a significantly increased risk of endometriosis or stage III/IV endometriosis in women who had a history of (primary) infertility. Pelvic signs (uterosacral/cul-de-sac tenderness and nodularity) Evidence from 1 study (n=429, moderate risk of bias) showed that there was a significantly increased risk of endometriosis in women with uterosacral/cul-de-sac tenderness and nodularity.
Recommendations	**5.** Suspect endometriosis in women (including young women aged 17 and under) presenting with 1 or more of the following symptoms or signs: • chronic pelvic pain • period-related pain (dysmenorrhoea) affecting daily activities and quality of life • deep pain during or after sexual intercourse • period-related or cyclical gastrointestinal symptoms, in particular, painful bowel movements • period-related or cyclical urinary symptoms, in particular, blood in the urine or pain passing urine • infertility in association with 1 or more of the above. **6.** Inform women with suspected or confirmed endometriosis that keeping a pain and symptom diary can aid discussions. **7.** Offer an abdominal and pelvic examination to women with suspected endometriosis to identify abdominal masses and pelvic signs, such as reduced organ mobility and enlargement, tender nodularity in the posterior vaginal fornix, and visible vaginal endometriotic lesions. **8.** If a pelvic examination is not appropriate, offer an abdominal examination to exclude abdominal masses.

Referral and monitoring

Table App 4 NICE 2017 Guideline evidence statements and recommendations: Referral and monitoring

Content	Description
Review question	How and when should women with endometriosis be monitored and referred for the following symptoms or condition progression and complications: • pelvic pain disrupting daily activities • cyclical bowel pain • cyclical voiding pain
Signs & symptoms to be considered	Pelvic pain disrupting daily activities; cyclical bowel pain; cyclical voiding pain
Critical outcomes	Confirmed diagnosis of endometriosis at follow-up; severity of endometriosis; referral to diagnostic services
GRADE rating	*Related to prognostic question on signs and symptoms – GRADE not used*
Clinical evidence statements	*Related to evidence statements for signs and symptoms*
Recommendations	**9.** Consider referring women to a gynaecology service for an ultrasound or gynaecology opinion if: • they have severe, persistent or recurrent symptoms of endometriosis • they have pelvic signs of endometriosis or • initial management is not effective, not tolerated or is contraindicated. **10.** Refer women to a specialist endometriosis service (endometriosis centre) if they have suspected or confirmed deep endometriosis involving the bowel, bladder or ureter. **11.** Consider referring young women (aged 17 and under) with suspected or confirmed endometriosis to a paediatric and adolescent gynaecology service, gynaecology service or specialist endometriosis service (endometriosis centre), depending on local service provision. **12.** Consider outpatient follow-up (with or without examination and pelvic imaging) for women with confirmed endometriosis, particularly women who choose not to have surgery, if they have: • deep endometriosis involving the bowel, bladder or ureter or • 1 or more endometrioma that is larger than 3 cm.

Diagnosis of endometriosis

Table App 5 NICE 2017 Guideline evidence statements and recommendations: Diagnosis of endometriosis

Content	Description
Ultrasound	
Review question	What is the accuracy of ultrasound in diagnosing endometriosis?
Index tests	Ultrasound (visual): transabdominal, transvaginal, rectal scanning
Critical outcomes	Sensitivity, specificity, QoL
GRADE rating	Very low – low
Clinical evidence statements	Pelvic endometriosis **Very low quality evidence** from 5 studies (n=1,222, includes TVUS, tg-TVUS and kissing ovaries sign) found that the pooled sensitivity and specificity of ultrasound was 62% (18% to 94%) and 93% (78% to 99%). Bowel endometriosis **Very low quality evidence** from 3 studies (n=314, includes TVUS, RWC-TVUS and TVUS-BP) found the pooled sensitivity and specificity of 88% (70% to 97%) and 95% (85% to 99%). Very low quality evidence from 2 studies (n=171, includes TRUS) showed sensitivity and specificity of 88% (47% to 100%) and 96% (89% to 99%) and 97% (82% to 100%) and 100% (94% to 100%), respectively. Deeply infiltrating endometriosis (DIE) **Very low quality evidence** from 3 studies (n=282, includes TVUS, TVUS-BP and 3D-TVUS) found that the pooled sensitivity and specificity of ultrasound was 78% (37% to 97%) and 90% (58% to 99%). Posterior DIE **Very low quality evidence** from 7 studies (n=853, includes TVUS, tg-TVUS and SVG) showed that the pooled sensitivity and specificity of ultrasound was 73% (55% to 8%7) and 91% (76% to 98%). Another 2 studies (n=248, includes SVG and 3D-TVUS) found sensitivity of 91% (75% to 98%) and 7% (78% to 93%) and specificity of 86% (57% to 98%) and 94% (87% to 97%), respectively. Anterior DIE **Low quality evidence** from 1 study (n=88) found sensitivity and specificity of TVUS of 33% (13% to 59%) and 100% (95% to 100%). Rectovaginal endometriosis **Very low quality evidence** from 10 studies (n=983, includes TVUS, TVUS-BP, tg-TVUS, introital 3D-US and SVG) found that the pooled sensitivity and specificity of ultrasound was 66% (33% to 90%) and 98% (95% to 99%). Low quality evidence from 1 study (n=90) that used RWC-TVUS reported sensitivity of 97% (90% to 100%) and specificity of 100% (84% to 100%). Very low quality evidence from 2 studies (n=232, includes TRUS) found that the sensitivity and specificity of ultrasound was 18% (2% to 52%) and 97% (85% to 100%) and 95% (88% to 99%) and 96% (91% to 99%), respectively. Rectosigmoid endometriosis **Very low quality evidence** from 14 studies (n=1615, includes TVUS, TVUS-BP, tg-TVUS, RWC-TVUS and SVG) found that the pooled sensitivity and specificity of ultrasound was 89% (80% to 95%) and 96% (93% to 98%), respectively. 1 study (n=202, includes 3D-TVUS) reported sensitivity of 91% (82% to 96%) and specificity of 97% (92% to 99%). Evidence was of low quality. Very low quality evidence from 4 studies (n=330, includes TRUS) found the pooled sensitivity and specificity of 90% (77% to 98%) and 93% (79% to 99%). Uterosacral ligament endometriosis **Very low quality evidence** from 7 studies (n=714, includes TVUS, tg-TVUS, TVUS-BP and SVG) found that the pooled sensitivity of ultrasound was 63% (45% to 79%) and the pooled specificity was 96% (91% to 98%). 2 studies (n=232, includes TRUS) reported sensitivity and specificity of 48% (37% to 59%) and 80% (44% to 97%) and 44% (14% to 79%) and 98% (93% to 100%), respectively. Vaginal wall involvement **Very low quality evidence** from 6 studies (n=679, includes TVUS, TVUS-BP, tg-TVUS and SVG) found that the pooled sensitivity and specificity of ultrasound was 57% (26% to 84%) and 98% (94% to 100%). **Very low quality evidence** from a further 2 studies (n=232) that used TRUS reported sensitivity of 7% (1% to 22%) and 100% (79% to 100%) and specificity of 100% (94% to 100%) and 100% (97% to 100%), respectively. Pouch of Douglas **Very low quality evidence** from 6 studies (n=755, includes TVUS, TVUS-BP and SVG+TVUS-BP) found that the pooled sensitivity and specificity of ultrasound was 83% (71% to 91%) and 97% (93% to 99%). Bladder endometriosis **Very low quality evidence** from 5 studies (n=383, includes TVUS, TVUS-BP, tg-TVUS, 3D-TVUS and SVG+TVUS-BP) reported the pooled sensitivity of 35% (13% to 63%) and specificity of 98% (96% to 100%). Ovarian endometriosis **Low quality evidence** from 9 studies (n=1066, includes TVUS, TVUS-BP and tg-TVUS) showed the pooled sensitivity of 90% (83% to 96%) and specificity of 96% (93% to 98%). One study (n=92, includes TRUS) reported sensitivity of 89% (74% to 97%) and specificity of 77% (64% to 87%).

Content	Description
Recommendations	General principle **17.** Do not exclude the possibility of endometriosis if the abdominal or pelvic examination, ultrasound or MRI are normal. If clinical suspicion remains or symptoms persist, consider referral for further assessment and investigation. Ultrasound **18.** Consider transvaginal ultrasound: • to investigate suspected endometriosis even if the pelvic and/or abdominal examination is normal • to identify endometriomas and deep endometriosis involving the bowel, bladder or ureter. **19.** If a transvaginal scan is not appropriate, consider a transabdominal ultrasound scan of the pelvis.
Biomarkers	
Review question	What is the accuracy of serum CA-125 in diagnosing endometriosis? What is the accuracy of HE-4 in diagnosing endometriosis? What is the accuracy of biomarkers in endometrial tissue, such as the nerve fibre marker PGP 9.5 in diagnosing endometriosis?
Index tests	CA125 (cut-off ≥35U/mL), HE- 4, biomarkers in endometrial tissues (the nerve fibre marker PGP 9.5)
Critical outcomes	Sensitivity, specificity, QoL
GRADE rating	Very low – moderate
Clinical evidence statements	**Very low quality evidence** from 24 studies (n=2491) showed that sensitivity and specificity of **serum CA125** in detecting endometriosis was 38% (30% to 47%) and 92% (89% to 94%). **Moderate quality evidence** from 1 study (n=101) showed that sensitivity and specificity of **serum CA125** in detecting endometrioma was 59% (39% to 76%) and 79% (68% to 88%). **Very low quality evidence** from 1 study (n=68) showed that at a cut off threshold of 114pM, specificity of **HE-4** in diagnosing endometriosis/endometrioma in women with diagnosis of pelvic mass was 98% (90% to 100%) and sensitivity was 0%. **Very low quality evidence** from 8 studies (n=429) reported that sensitivity and specificity of PGP 9.5 for detection of endometriosis was 88% (69% to 98%) and 81% (69% to 91%).
Recommendations	**20.** Do not use serum CA125 to diagnose endometriosis. **21.** If a coincidentally reported serum CA125 level is available, be aware that: • a raised serum CA125 (that is, 35 IU/ml or more) may be consistent with having endometriosis • endometriosis may be present despite a normal serum CA125 (less than 35 IU/ml). *No recommendation was made regarding Biomarker Human Epididymis protein 4* *No recommendation was made regarding biomarkers in endometrial tissues*
MRI	
Review question	What is the accuracy of MRI in diagnosing endometriosis?
Index test	Pelvic MRI
Critical outcomes	Sensitivity, specificity, QoL
GRADE rating	Very low
Clinical evidence statements	Pelvic endometriosis Eight studies (n=333, includes conventional (T1-/T2-w), T1-w+fat-suppressed, T-1/T2-w + fat-suppressed/Gd and 3.0T MRI) reported that the pooled sensitivity and specificity of MRI was 77% (62% to 88%) and 72% (53% to 87%). Two studies (n=62, includes T1-/T2-w + fat-suppressed and fat-suppressed MRI) showed sensitivity and specificity of 86% (64% to 97%) and 76% (56% to 90%), 50% (19% to 81%) and 100% (16% to 100%), respectively. One study (n=31, includes T-1/T2-w + fat-suppressed/Gd MRI) found sensitivity of 81% (58% to 95%) and specificity of 50% (19% to 81%). Evidence was of **very low quality**. DIE **Very low quality evidence** from 4 studies (n=212, includes T-1/T2-w + fat-suppressed/Gd and 3.0T MRI) found that the pooled sensitivity and specificity of MRI was 96% (90% to 99%) and 86% (54% to 98%). Posterior DIE **Very low quality evidence** from 2 studies (n=54, includes Jelly method (T1-/T2-w + fat-suppressed) and 2D FSE T2-w MRI) reported that the sensitivity and specificity of MRI was 89% (65% to 99%), 94% (71% to 100%), and 20% (1% to 72%) and 100% (77% to 100%), respectively. Very low quality from 1 study (n=23, includes 3D MRI) found sensitivity of 100% (81% to 100%) and specificity of 20% (1% to 72%). Anterior DIE **Very low quality evidence** from 1 study (n=41, includes 3.0T MRI) reported the sensitivity of MRI in diagnosing anterior DIE of 75% (35% to 97%) and specificity of 100% (89% to 100%). Rectovaginal endometriosis **Very low quality evidence** from 3 studies (n=288, includes T-1/T2-w + fat-suppressed/Gd MRI) found that the pooled sensitivity and specificity of MRI was 75% (35% to 95%) and 88% (43% to 99%).

Content	Description
	Rectosigmoid endometriosis **Very low quality evidence** from 6 studies (n=662, includes T-1/T2-w + fat-suppressed/Gd, 2D FSE T2-w, jelly method (T1-/T2-w + fat-suppressed) and 3.0T MRI) found that the pooled sensitivity and specificity of MRI was 91% (79% to 97%) and 96% (92% to 99%). Very low quality evidence from 1 study (n=23, includes 3D MRI) reported sensitivity of 85% (55% to 98%) and specificity of 90% (55% to 100%). Uterosacral ligament endometriosis **Very low quality evidence** from 5 studies (n=241, includes T-1/T2-w + fat-suppressed/Gd, 2D FSE T2-w and 3.0T MRI) found that the pooled sensitivity of MRI was 88% (77% to 96%) and the pooled specificity was 84% (62% to 96%). Very low quality evidence from 1 study (n=23, includes 3D MRI) reported sensitivity and specificity of 88% (64% to 99%) and of 33% (4% to 78%). Vaginal wall involvement **Very low quality evidence** from 4 studies (n=248, includes T-1/T2-w + fat-suppressed/Gd, 2D FSE T2-w and 3.0T MRI) found that the pooled sensitivity and specificity of MRI was 75% (50% to 92%) and 94% (83% to 99%). Very low quality evidence from 1 study (n=23, includes 3D MRI) reported sensitivity of 80% (28% to 99%) and specificity of 100% (81% to 100%). Pouch of Douglas **Very low quality evidence** from 5 studies (n=154, includes jelly method (T1-/T2-w + fat-suppressed), 2D FSE T2-w and 3.0T MRI) found that the pooled sensitivity and specificity of MRI was 89% (75% to 97%) and 91% (76% to 98%). Very low quality evidence from 1 study (n=23, includes 3D MRI) reported sensitivity of 71% (42% to 92%) and specificity of 100% (66% to 100%). Ureteral endometriosis **Very low quality evidence** from 1 study (n=92, includes T1-/T2-w + fat-suppressed/Gd MRI) reported sensitivity of 50% (16% to 84%) and specificity of 100% (96% to 100%). Bladder endometriosis **Very low quality evidence** from 1 study (n=92, includes T1-/T2-w + fat-suppressed/Gd MRI) found sensitivity of 23% (5% to 54%) and specificity of 100% (95% to 100%). Ovarian endometriosis **Very low quality evidence** from 3 studies (n=179, includes T1-/T2-w + fat-suppressed/Gd and 3.0T MRI) found that the pooled sensitivity and specificity of MRI was 93% (78% to 99%) and 92% (73% to 99%).
Recommendations	**22.** Do not use pelvic MRI as the primary investigation to diagnose endometriosis in women with symptoms or signs suggestive of endometriosis. **23.** Consider pelvic MRI to assess the extent of deep endometriosis involving the bowel, bladder or ureter. **24.** Ensure that pelvic MRI scans are interpreted by a healthcare professional with specialist expertise in gynaecological imaging.
Surgical diagnosis	
Review question	What is the accuracy of surgery with or without histological confirmation in diagnosing endometriosis?
Index test	Surgical diagnosis with or without histological confirmation
Critical outcomes	Sensitivity, specificity, QoL
GRADE rating	*Diagnostic question and no appropriate reference standard – GRADE not used.* *17 identified studies were assessed as having very high to moderate risk of bias*
Clinical evidence statements	Endometriosis Two **moderate and high risk of bias** studies reported similar findings regarding sensitivity and specificity: 97% (90% to 100%) and 98% (95% to 99%), and 77% (95%CI: 72% to 82%) and 79% (95%CI: 76% to 82%), respectively. Biopsies In studies with **very high to high risk of bias**, where no sensitivity and specificity were reported, the papers only reported positive test results, i.e. where results of histology matched the positive surgical diagnosis. The results were highly variable. The positive test result ranged from 53% to 93% (based on the number of biopsies). The median of visual diagnosis confirmed histologically was 58.5% based on biopsies (n=11 studies). Number of patients In studies, where positive test values were presented based on the number of patients, the positive test range was between 42% and 97%. The median of visual diagnosis confirmed histologically was 75.5% based on the number of patients (n=13 studies). Endometrioma A **very high risk of bias** study reported a sensitivity of 97% (94% to 99%) and a specificity of 95% (90% to 99%) (based on the number of ovarian cysts). The positive and negative test results, i.e. where results of histology matched the positive or negative surgical diagnosis, were 98% and 94%, respectively.

Content	Description
Recommendations	**25.** Consider laparoscopy to diagnose endometriosis in women with suspected endometriosis, even if the ultrasound was normal. **26.** For women with suspected deep endometriosis involving the bowel, bladder or ureter, consider a pelvic ultrasound or MRI before an operative laparoscopy. **27.** During a diagnostic laparoscopy, a gynaecologist with training and skills in laparoscopic surgery for endometriosis should perform a systematic inspection of the pelvis. **28.** During a diagnostic laparoscopy, consider taking a biopsy of suspected endometriosis: • to confirm the diagnosis of endometriosis (be aware that a negative histological result does not exclude endometriosis) • to exclude malignancy if an endometrioma is treated but not excised. **29.** If a full, systematic laparoscopy is performed and is normal, explain to the woman that she does not have endometriosis, and offer alternative management.

Abbreviations: 2D, two-dimensional; 3D, three-dimensional; BP, bowel preparation; CA, cancer antigen; DIE, deeply infiltrating endometriosis; FSE, fast spin echo; Gd, gadolinium; HE, human epididymis protein; MRI, magnetic resonance imaging; PGP, Protein Gene Product; QoL, quality of life; RWC, rectal water contrast; SVG, sonovaginography; TRUS, transrectal ultrasound; TVUS, transvaginal ultrasound.

Staging systems

Table App 6 NICE 2017 Guideline evidence statements and recommendations: Staging systems

Content	Description
Review question	What is the effectiveness of using endometriosis-staging systems to guide treatment of endometriosis?
Interventions in scope	Revised American Society for Reproductive Medicine (rASRM) staging system Revised American Fertility Society classification system (rAFS) Enzian (for staging of deep infiltrating endometriosis only) Enzian plus rASRM Endometriosis Fertility Index (EFI) Surgical staging *Exclude non-validated scales*
Critical outcomes	Pain, QoL, effect on daily activities
GRADE rating	No clinical evidence identified
Clinical evidence statements	*Not applicable.* *"The Committee concluded that current staging systems cannot guide decisions about treatments because there is no clear correlation between stage and severity of symptoms (for example, severe pain and low stage). The Committee agreed treatment decisions need to be based on the symptoms and be tailored to individual needs, preferences and priorities in terms of pain and fertility preservation."*
Recommendations	**30.** Offer endometriosis treatment according to the woman's symptoms, preferences and priorities, rather than the stage of the endometriosis. **31.** When endometriosis is diagnosed, the gynaecologist should document a detailed description of the appearance and site of endometriosis.

Abbreviations: QoL, quality of life.

Pharmacological pain management

Table App 7 NICE 2017 Guideline evidence statements and recommendations: Pharmacological pain management

Content	Description
Analgesics	
Review question	What is the effectiveness of analgesics for reducing pain in women with endometriosis, including recurrent and asymptomatic endometriosis?
Interventions in scope	NSAIDs of any type and administered at any dose, frequency, treatment duration, or by any type of administration Non-opioid analgesics (paracetamol) NSAIDs and COX-2 inhibitors (diclofenac, ibuprofen, naproxen, celecoxib, mefenamic acid, etoricoxib, indomethacin, tolfenamic acid, aspirin (in doses greater than 600 mg)) Compound analgesics (co-codamol, co-codaprin, co-dydramol) Opioid analgesics (codeine, dihydrocodeine, tramadol, buprenorphine)
Critical outcomes	Pain, QoL, effect on daily activities
GRADE rating	Very low
Clinical evidence statements	**Very low quality evidence** from 1 crossover RCT (n=20) showed that there was no difference in overall pain relief, unintended effects or need for supplementary analgesia when women with endometriosis received naproxen sodium compared to placebo for 2 menstrual cycles, although there was uncertainty around the estimate.
Recommendations	**32.** For women with endometriosis-related pain, discuss the benefits and risks of analgesics, taking into account any comorbidities and the woman's preferences. **33.** Consider a short trial (for example, 3 months) of paracetamol or an NSAID alone or in combination for first-line management of endometriosis-related pain. **34.** If a trial of paracetamol or an NSAID (alone or in combination) does not provide adequate pain relief, consider other forms of pain management and referral for further assessment.
Neuromodulators	
Review question	What is the effectiveness of neuromodulators for treating endometriosis, including recurrent and asymptomatic endometriosis?
Interventions in scope	Neuromodulators (neuropathic analgesia) of any type and administered at any dose, frequency, treatment duration, or by any type of administration. Tricyclics (amitriptyline, nortriptyline) SNRIs (duloxetine, mirtazapine, venlafaxine) Local anaesthetics (lidocaine – topical and infusion) Capsaicin patches NMDA antagonist (ketamine) Anticonvulsants (gabapentin, pregabalin, tiagabine, carbamazepine, phenytoin, valproate topiramate) Nerve blocks *Exclude nerve ablation (LUNA is covered by a NICE Interventional Procedure Guideline with the following recommendation: The evidence on LUNA for chronic pelvic pain suggests that it is not efficacious and therefore should not be used)*
Critical outcomes	Pain, QoL, effect on daily activities
GRADE rating	Very low – low
Clinical evidence statements	No evidence was identified that addressed the effectiveness of commonly used neuropathic analgesics. <u>Pertubation of lidocaine vs. placebo</u> *Pain up to 12 months* **Very low to low quality evidence** from 1 RCT with 42 women with endometriosis suggested higher rates of women who reported a significant improvement in pain associated with pertubation of lidocaine compared to placebo at 3, 6, 9 and 12 months. However the uncertainty around this improvement was too large to draw clear conclusions about its clinical effectiveness. *EHP-30* **Very low quality evidence** from 1 RCT with 42 women with endometriosis reported no clear differences between women treated with lidocaine compared to placebo at 6 and 12 months for the subscales pain, control and powerlessness, emotional well-being, self-image and sexual intercourse. A small difference on the social support subscale was reported at 6 but not 12 months. *Recurrence at 12 months* **Very low quality evidence** from 1 RCT (N=42) suggested a higher rate of recurrence in those receiving lidocaine compared to those in the placebo group. However, the uncertainty around this effect was too large to draw clear conclusions about this finding. *Escalating levels of pain with a need for other therapies at 12 months*

Content	Description
	Very low quality evidence from 1 RCT (N=42) suggested that there were fewer women needing other treatments in the lidocaine group compared to the control group. However, there was too much uncertainty around this effect to draw clear conclusions from these findings Pertubation of bipuvacaine vs. Placebo *Pain up to 3 months* **Moderate to high quality evidence** from 1 RCT conducted with 60 women who have endometriosis reported improvements in pain at 1, 2 and 3 months associated with bipuvacaine pertubation. However, the uncertainty around this effect make it difficult to draw conclusions about the clinical significance of this finding. *Satisfaction with treatment at 3 months* **High quality evidence** from 1 RCT conducted with 60 women who have endometriosis showed a higher rate of satisfaction with bipuvacaine treatment compared to placebo.
Recommendations	**35.** For recommendations on using neuromodulators to treat neuropathic pain, see the NICE guideline on neuropathic pain.
Hormonal treatments	
Review question	What is the effectiveness of hormonal medical treatments for treating endometriosis compared to placebo, other hormonal medical treatments, usual care, surgery, or surgery in combination with hormonal treatment?
Interventions in scope	Danazol (high dose 400-800 mg/d; low dose 100-400 mg/d) Gestrinone Oestrogens (oestradiol oral 1-2 mg/d; conjugated equine oestrogens oral 0.3-1.25 mg/d) Progestogens (lynestrenol; norethindrone/norethisterone [2.5 mg/d]; gestodene [i.m 5-10 mg]; desogestrel [oral 75 ug/d]; medroxyprogesterone [low dose oral 15-20 mg/d, high dose oral 20-30 mg/d, i.m 150 mg/3m, s.c. 104 mg/3m]; levonorgestrel [oral 30 ug/d, mirena coil 20 ug/d released over 5 years]; promegestone [sc. 68 mg released over 3 years]; dienogest [2 mg/d]) GnRH agonists (nafarelin [nasal spray – 200 ug/12h); leuprorelin acetate [depot – 3.75 mg/m]; goserelin [s.c – 3.6 mg/m]; triptorelin/dipherelin [i.m 3 mg/m]; buserelin [300 ug/8h]) Anti-androgens/progestogens (cyproterone acetate [10-12.5 mg/d, only in combination as COC]) Aromatase inhibitors (anazstrozole [oral 1 mg/d]; letrozole [oral 2.5 mg/d]) Selective oestrogen receptor modulators (raloxifene [60 mg/d]) Selective progestogen receptor modulators (tibolone [oral 2.5 mg/d])
Critical outcomes	Pain relief, HRQoL, discontinuation of treatment due to adverse events
GRADE rating	Very low – high
Clinical evidence statements	Comparison 1: GnRH agonist versus no treatment *Pain* **Very low quality evidence** from 1 trial (n=35) found a clinically significant beneficial effect of GnRH agonist treatment (buserelin IN) compared with expectant management for dysmenorrhoea relief (measured using VAS) at 12 weeks after starting treatment. Comparison 2: GnRH agonist versus placebo *Dysmenorrhoea* **Moderate quality evidence** from 1 trial (n=88) demonstrated a clinically significant beneficial effect of GnRH agonist treatment (leuprorelin IM depot) compared with placebo in the reduction of dysmenorrhoea (measured using VAS) at 12 weeks after starting treatment. *Pelvic pain* **Moderate quality evidence** from 1 trial (n=88) demonstrated a clinically significant beneficial effect of GnRH agonist treatment (leuprorelin IM depot) compared with placebo in the reduction of pelvic pain (measured using VAS) at 12 weeks after starting treatment. **Moderate quality evidence** from 1 trial (n=46) found a clinically significant beneficial effect of GnRH agonist treatment (triptorelin IM depot) compared with placebo in the cessation of pelvic tenderness at 6 months after starting treatment. *Dyspareunia* **Moderate quality evidence** from 1 trial (n=88) demonstrated a clinically significant beneficial effect of GnRH agonist treatment (leuprorelin IM depot) compared with placebo in the reduction of deep dyspareunia (measured using VAS) at 12 weeks after starting treatment. **Very low quality evidence** from 1 trial (n=46) found a clinically significant difference between GnRH agonist treatment (triptorelin IM depot) and placebo in the cessation of pelvic tenderness at 6 months after starting treatment. Comparison 3: Combined oral contraceptive pill versus placebo *Pain* **Low and moderate quality evidence** from 1 trial (n=96) found a clinically significant beneficial effect of treatment with a combined oral contraceptive compared with placebo for dysmenorrhoea (measured using VAS), but no clinically significant difference between treatments for non-menstrual pelvic pain score (measured using VAS) or induration. Comparison 4: GnRH agonist versus danazol *Pain*

Content	Description
	Moderate quality evidence from 1 RCT (n=59) found no clinically significant difference between GnRH agonist treatment (nafarelin IN) compared with danazol for pelvic tenderness and pelvic induration at 3 months (during treatment period) and at the end of the 6 month treatment period. *Patient requiring surgery because of reappearance of symptoms and positive findings at pelvic examination* **Moderate quality evidence** from 1 RCT (n=62) reported no clinically significant difference between GnRH agonist treatment (buserelin IN) and danazol in the number of patients requiring surgery because of reappearance of symptoms and positive findings at pelvic examination at follow-up at least 12 months after treatment ended. *Quality of life* **Low quality evidence** from 1 RCT (n=169) found no statistically significant difference in quality of life (PGWBI and modified Nottingham Health Profile) between GnRH agonist (nafarelin IN) and danazol at the end of the 6 month treatment period. Clinical significance was not calculable as the data reported in the paper were descriptive. Comparison 5: GnRH agonist versus levonorgestrel-releasing intrauterine system *Quality of life* **Moderate quality evidence** from 1 RCT (n=83) reported no clinically significant difference between GnRH agonist treatment (leuprolide IM) and levonorgestrel-releasing intrauterine system in quality of life (PGWBI) at the end of the 6 month treatment period. Comparison 6: GnRH agonist versus DMPA-SC *Effect on daily activities* **High to moderate quality evidence** from 1 RCT (n=274) found no clinically significant difference between GnRH agonist treatment (leuprolide IM) and depot MPA (given by SC injection) regarding the mean number of hours of productivity lost at employment and housework at the end of the 6 month treatment period and at 18 months (12 months post-treatment). Comparison 7: GnRH agonist 1 + placebo versus GnRH agonist 2 + placebo *Pain* **Low quality evidence** from 1 RCT (n=192) found no clinical significant differences between GnRH agonist treatments (nafarelin 200 ug BDS IN and IM placebo compared with leuprolide depot 3.75 mg IM plus IN placebo) for pelvic tenderness and pelvic induration at 6 months after the end of the treatment period. Comparison 8: GnRH agonist + placebo versus progestin + placebo *Quality of life* **Very low quality evidence** from 1 RCT (n=48) reported no clinical significant differences between treatment with a GnRH agonist (nafarelin 200 µg IN BDS) and oral placebo compared with oral medroxyprogesterone (BDS 15 mg) and IN placebo in terms of overall quality of life (measured using Goldberg's general health and Nottingham Health Profile Questionnaire) at 6 months after the end of the treatment period. Results were poorly reported. *Effect on daily activities* Very low quality evidence from 1 trial (n=48) reported no clinical significant differences between treatment with a GnRH agonist (nafarelin 200 µg IN BDS) and oral placebo compared with oral medroxyprogesterone (BDS 15 mg) and IN placebo in terms of the effects on daily activities (measured using the Coping wheel, Inventory of Social Support and Interaction – ISSI and demands, control and support questionnaires) including sleep disturbances, anxiety-depression, household work, vacation life and leisure, sexual life, motivation, emotional balance and work activities (including psychological work demands, intellectual discretion at work, authority over decisions at work and social support) at 6 months after the end of the treatment period. Results were poorly reported. Comparison 9: GnRH agonist + placebo versus danazol + placebo *Pain* **Very low quality evidence** from 1 RCT (n=49) found no clinically significant difference between GnRH agonist treatment (nafarelin 200 mcg BDS -400 mcg/d- IN) and oral placebo compared with oral danazol (200 mg TDS) plus IN placebo for pelvic tenderness and pelvic induration at 6 months after the end of the treatment period. **Very low quality evidence** from 1 RCT (n=96) found no clinically significant differences between GnRH agonist treatment (nafarelin 200 mcg BDS -400 mcg/d- IN) and oral placebo compared with danazol (200 mg TDS) plus IN placebo for pelvic tenderness and pelvic induration at 12 months after the end of the treatment period. **Low quality evidence** from 1 RCT (n=253) found no clinically significant difference between GnRH agonist treatment (leuprolide 3.75 mg monthly IM) and oral placebo compared with oral danazol (800 mg once daily) plus IM placebo for pelvic tenderness at 6 months after the end of the treatment period. Comparison 10: Depot medroxyprogesterone acetate versus cOCP + danazol *Pain* **Moderate quality evidence** from 1 RCT (n=80) found a clinically significant beneficial effect of depot medroxyprogesterone acetate treatment compared with cOCP plus danazol for dysmenorrhoea at 6 months after starting treatment and at the end of the treatment period (at 12 months). **Very low- to low-quality evidence** from the same study reported no clinically significant difference between the 2 intervention groups for dyspareunia and non-menstrual pelvic pain at 6 months after starting treatment and at the end of the treatment period (at 12 months). *Patient satisfaction* **Low quality evidence** from the same RCT (n=80) reported no clinically significant difference between depot medroxyprogesterone acetate treatment compared with cOCP plus danazol regarding patient satisfaction with treatment (very satisfied/satisfied) at the end of the treatment period (at 12 months). Comparison 11: GnRH agonist (triptorelin) + E/P pill versus E/P pill *Pain*

Content	Description
	One RCT (n=102) reported a clinically significant beneficial effect of GnRH agonist (triptorelin) + E/P pill (gestodene 0.75 mg/ethinylestradiol 0.03 mg) treatment compared with E/P pill (gestodene 0.75 mg/ethinylestradiol 0.03 mg) alone for dysmenorrhoea and non-menstrual pelvic pain at 8 months during the treatment period and for dysmenorrhoea at the end of the treatment period (at 12 months). Evidence was of **low to moderate quality**. **Low quality evidence** from the same study found no clinically significant beneficial effect of E/P pill (gestodene 0.75 mg/ethinylestradiol 0.03 mg) compared with GnRH agonist (triptorelin) + E/P pill (gestodene 0.75 mg/ethinylestradiol 0.03 mg) treatment for non-menstrual pelvic pain at the end of treatment period (at 12 months). Comparison 12: GnRH agonist (goserelin) versus cOCP *Pain* **Low quality evidence** from 1 RCT (n=57) demonstrated a clinically significant beneficial effect of GnRH agonist (goserelin) treatment compared with cOCP (0.02 mg ethinylestradiol and 0.15 mg desogestrel) for dyspareunia at the end of the treatment period (at 6 months). The same study reported no clinically significant difference between the 2 study arms for non-menstrual pelvic pain and dysmenorrhoea at the end of the treatment period (at 6 months) and for dyspareunia, non-menstrual pelvic pain and dysmenorrhoea at 6 months after the treatment period. Evidence was of **very low to low quality**.
Recommendations	**36.** Explain to women with suspected or confirmed endometriosis that hormonal treatment for endometriosis can reduce pain and has no permanent negative effect on subsequent fertility. **37.** Offer hormonal treatment (for example, the combined oral contraceptive pill or a progestogen)[79] to women with suspected, confirmed or recurrent endometriosis. **38.** If initial hormonal treatment for endometriosis is not effective, not tolerated or is contraindicated, refer the woman to gynaecology service, specialist endometriosis service (endometriosis centres) or paediatric and adolescent gynaecology service for investigation and treatment options.

Abbreviations: BDS, twice per day; cOC, combined oral contraceptive; cOCP, combined oral contraceptive pill; COX, cyclooxygenase; DPMA, depot medroxyprogesterone acetate; E/P, ethinylestradiol pill; GnRH, gonadotropin releasing hormone; HRQoL, health-related quality of life; IM or i.m., intramuscular; IN, intravenous; ISSI, Inventory of Social Support and Interaction; LUNA, laparoscopic uterine nerve ablation; MPA, medroxyprogesterone acetate; NICE, National Institute for Health and Clinical Excellence; NMDA, N-methyl-D-aspartate; NSAID, non-steroidal anti-inflammatory drug; PGWBI, Psychological General Well Being Index; QoL, quality of life; RCT, randomised controlled trial; SC or s.c., subcutaneous; SNRI, serotonin–norepinephrine reuptake inhibitor; TDS, three times per day; VAS, visual analog scale.

[79] At the time of publication (September 2017), not all combined oral contraceptive pills or progestogens have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

Non-pharmacological management

Table App 8 NICE 2017 Guideline evidence statements and recommendations: Non-pharmacological management

Content	Description
Review question	What is the effectiveness of non-pharmacological therapies (for example, acupuncture) for managing pain associated with endometriosis?
Interventions in scope	Behavioural medicine (cognitive behavioural therapy; mindfulness; relaxation techniques' pain management programs; pain management physiotherapy; pain management psychology; expert patient program; exercise [e.g. yoga, pilates]; hypnosis; psychosexual therapy; biofeedback) Physical methods (acupuncture; TENS; manual and physical therapy; massage [e.g. shiatsu]; osteopathy; chiropractic treatment; reflexology) Other (herbal medicine; naturopathy; homeopathic therapy; nutrition [gluten free; dairy free; vegetarian; endo diet])
Critical outcomes	Pain (measured by Biberoglu and Behrman scale or other scale with identical subscales), pain measured by a VAS, QoL (measured using the SF-36), discontinuation of treatment due to adverse effects, adherence to treatment program
GRADE rating	Very low – low
Clinical evidence statements	<u>Comparison 1: Conventional OCP and Dan'e Chinese herbal medicine vs. no treatment</u> *Fertility* **Low and moderate quality evidence** from 1 RCT (n=156) found no clinically significant difference in incidence in live birth or miscarriage at 12 months after treatment ended when use of cOCP and Dan'e CHM in combination was compared to no treatment. <u>Comparison 2: Conventional OCP and Dan'e Chinese herbal medicine vs. conventional OCP</u> *Fertility* **Low and moderate quality evidence** from 1 RCT (n=156) found no clinically significant difference in incidence in live birth or miscarriage at 12 months after treatment ended when use of cOCP and Dan'e CHM in combination was compared to use of cOCP alone. <u>Comparison 3–5: Dietary supplements vs. placebo, dietary supplements vs. GnRH agonist and dietary supplements vs. conventional OCP</u> *Recurrence rates* **Low quality evidence** from 1 RCT (n=240) found no clinically significant difference in endometrioma recurrence at 18 months after surgery when postoperative use of a 6 month course of dietary supplements (including vitamin, mineral and fatty acid supplementation) was compared to placebo, GnRH agonist (tryptorelin or leuprorelin) or a cOCP (continuous, low-dose). <u>Comparison 6: Acupuncture vs. sham acupuncture</u> *Pain* **Very low and low quality evidence** from 1 RCT (n=18) found a clinically significant improvement in pain reduction at 4 weeks during treatment when Japanese-style acupuncture was compared to sham acupuncture. However, there was no clinically significant difference between the 2 interventions for pain assessed at the end of 8 weeks of treatment and at 6 month follow-up. **Moderate quality evidence** from 1 RCT (n=42) found a clinically significant improvement in pain reduction for chronic pelvic pain and dyspareunia at 2 months after treatment when acupuncture was compared to sham acupuncture. *Quality of life* **Low quality evidence** from 1 RCT (n=18) found a clinically significant improvement in quality of life (EHP total score) at 4 weeks during treatment, at the end of 8 weeks of treatment and at 6 month follow-up when Japanese-style acupuncture was compared to sham acupuncture. **Low quality evidence** from 1 RCT (n=18) found no clinically significant difference in quality of life at 4 weeks during treatment (Pediatric QoL Inventory total score) when Japanese-style acupuncture was compared to sham acupuncture. There may be a clinically significant benefit of Japanese-style acupuncture compared to sham acupuncture for improvement in quality of life at the end of 8 weeks of treatment, but there is uncertainty around the estimate. However, there was a clinically significant improvement in quality of life at 6 month follow up when Japanese-style acupuncture was compared to sham acupuncture. *Activities of daily living* **Very low and low quality evidence** from 1 RCT (n=18) found a clinically significant benefit in improvement in activities of daily living at 4 weeks during treatment when Japanese-style acupuncture was compared to sham acupuncture. However, there was no clinically significant difference between the 2 interventions for activities of daily living assessed at the end of 8 weeks of treatment and at 6 months follow up. <u>Acupuncture vs. danazol</u> *Cure of symptoms* **Very low quality evidence** from 1 RCT (n=70) found no clinically significant difference in cure of endometriosis symptoms at 3 months post-treatment when use of abdominal acupuncture was compared to danazol over 3 menstrual cycles. <u>Comparison 8: Acupuncture vs. Chinese herbal medicine</u> *Dysmenorrhoea*

Content	Description
	Very low quality evidence from 1 RCT (n=67) found a clinically significant improvement in dysmenorrhoea at the end of 3 months treatment when use of ear acupuncture therapy was compared to oral administration of CHM. *Cure of symptoms* **Low quality evidence** from 1 RCT (n=67) found that there may be a clinically significant benefit at the end of 3 months treatment with ear acupuncture therapy compared to oral administration of CHM for cure of endometriosis symptoms, but there is uncertainty around the estimate. Comparison 9: Chinese herbal medicine (individualised decoction) vs. placebo *Pain and quality of life* **Very low and low quality evidence** from 1 RCT (n=33) found no clinically significant differences in pain symptoms (VAS) or quality of life (MYMOP and EHP 30) at the end of 16 weeks treatment with an individualised CHM decoction compared to a placebo decoction. Comparison 10: Chinese herbal medicine (Nei Yi pills) vs. danazol *Pain* **Low quality evidence** from 1 RCT (n=58) found clinically significant improvement in symptomatic relief within 3 years of stopping treatment. However, there was no clinically significant difference dysmenorrhoea score, lumbosacral pain relief, rectal irritation relief, tenderness of vaginal nodules in the posterior fornix at the end of 3 months treatment with CHM (Nei Yi pills) compared to danazol (**low quality evidence**). Reduction in the size and extent of endometriotic cysts **Very low quality evidence** from 1 RCT (n=58) found no clinically significant difference in disappearance or shrinkage of adnexal masses at the end of 3 months treatment with CHM (Nei Yi pills) compared to danazol. Comparison 11: Chinese herbal medicine (Nei Yi pills plus Nei Yi enema) vs. danazol *Pain* **Low quality evidence** from 1 RCT (n=58) found clinically significant benefit in symptomatic relief (within 3 years of stopping treatment) and reduction in dysmenorrhoea score at the end of 3 months treatment with CHM (Nei Yi pills plus Nei Yi enema) compared to danazol. There may be a clinically significant benefit of CHM (Nei Yi pills plus Nei Yi enema) compared to danazol for rectal irritation relief, but there is uncertainty around the estimate. No clinically significant differences in lumbosacral pain relief or in tenderness of vaginal nodules in the posterior fornix were identified when CHM (Nei Yi pills plus Nei Yi enema) and danazol were compared. *Reduction in the size and extent of endometriotic cysts* **Low quality evidence** from 1 RCT (n=58) found clinically significant benefit in disappearance or shrinkage of adnexal masses at the end of 3 months treatment with CHM (Nei Yi pills plus Nei Yi enema) compared to danazol. Comparison 12: Chinese herbal medicine (Nei Yi pills plus Nei Yi enema) vs. Chinese herbal medicine (Nei Yi pills) *Pain* **Very low and low quality evidence** from 1 RCT (n=58) found that there may be a clinically significant improvement in dysmenorrhoea at the end of 3 months treatment when CHM administered orally and rectally (Nei Yi pills plus Nei Yi enema) compared to oral administration of CHM alone (Nei Yi pills), but there is uncertainty around the estimate. No clinically significant differences in symptomatic relief, lumbosacral pain relief, rectal irritation relief or tenderness of vaginal nodules in posterior fornix were found when the 2 interventions were compared. *Reduction in the size and extent of endometriotic cysts* **Low quality evidence** from 1 RCT (n=58) found no clinically significant difference in disappearance or shrinkage of adnexal masses at the end of 3 months treatment when CHM administered orally and rectally (Nei Yi pills plus Nei Yi enema) and oral administration of CHM alone (Nei Yi pills) were compared. Comparison 13: Chinese herbal medicine (Gui-Zhi-Fu-Ling-Wan) and acupuncture vs. danazol *Pain* **Very low quality evidence** from 1 RCT (n=78) found no clinically significant differences in dysmenorrhoea, lumbosacral pain or dyspareunia at the end of 3 months treatment when use of CHM (Gui-Zhi-Fu-Ling-Wan) and acupuncture in combination was compared to danazol. Comparison 14: Acupuncture-like TENS vs. self-applied TENS *Quality of life* **Very low quality evidence** from 1 RCT (n=22) found no clinically significant difference in quality of life (EHP-30 total score) when use of acupuncture-like TENS was compared to self-applied TENS.
Recommendations	**39.** Advise women that the available evidence does not support the use of traditional Chinese medicine or other Chinese herbal medicines or supplements for treating endometriosis.

Abbreviations: CHM, Chinese herbal medicine; cOCP, conventional oral contraceptive pill; EHP, Endometriosis Health Profile; GnRH, gonadotropin releasing hormone; MYMOP, Measure Your own Medical Outcomes Profile; OCP, oral contraceptive pill; QoL, quality of life; RCT, randomised controlled trial; SF-36, 36-item Short Form Health Survey; TENS, transcutaneous electrical nerve stimulation; VAS, visual analog scale.

Surgical management

Table App 9 NICE 2017 Guideline evidence statements and recommendations: Surgical management and combination treatment

Content	Description
Surgery (including ablation and excision)	
Review question	What is the effectiveness of the following treatments for endometriosis, including recurrent and asymptomatic endometriosis: • surgery; • combined surgery and hormonal treatment?
Interventions in scope	Ablation Excision General techniques (robotic, laparoscopic, open excision, total peritoneal excision) Specific techniques (laser, diathermy, bi-polar and mono polar, ultrasonic energy or a combination i.e. ultrasonic with bi-polar) These may also include: ovarian cystectomy, drainage of endometriosis *Exclude helium coagulation*
Critical outcomes	Pain (measured by Biberoglu and Behrman scale or other scale with identical subscales), pain measured by a VAS, QoL (measured using the SF-36)
GRADE rating	Very low – high
Clinical evidence statements	**Endometriosis** <u>Laparoscopic treatment (excision or ablation) versus diagnostic laparoscopy for endometriosis</u> *Overall pain at 6 months* **Very low quality evidence** from 1 study of 69 women with endometriosis showed a clinically significant improvement in overall pain at 6 months associated with laparoscopic treatment compared with diagnostic laparoscopy for endometriosis. *Overall pain at 12 months* **Low quality evidence** from 1 study of 69 women with endometriosis found a clinically significant improvement in overall pain at 12 months associated with laparoscopic treatment compared with diagnostic laparoscopy for endometriosis. <u>Live birth or ongoing pregnancy</u> **Very low quality evidence** from 2 studies of 382 women found no clinically significant difference in live birth or ongoing pregnancy between laparoscopic treatment and diagnostic laparoscopy for endometriosis. <u>Clinical pregnancy</u> **Very low quality evidence** from 3 studies including 528 women with endometriosis found no clinically significant difference between laparoscopic treatment and diagnostic laparoscopy for the outcome of clinical pregnancy. <u>Miscarriage per pregnancy</u> **Very low quality evidence** from 2 studies including 112 women with endometriosis found no clinically significant difference between laparoscopic treatment and diagnostic laparoscopy for miscarriages per pregnancy. <u>Excision versus diagnostic laparoscopy for endometriosis</u> *Overall pain at 6 months* **High quality evidence** from 1 study including 39 women with endometriosis found a clinically significant improvement in overall pain at 6 months associated with excision compared with diagnostic laparoscopy. *Overall pain score at 6 months* **Very low quality evidence** from 1 study including 16 women with endometriosis found a clinically significant reduction in overall pain score at 6 months associated with diagnostic laparoscopy compared with excision. *Overall pelvic pain score at 12 months* **Moderate quality evidence** from 1 study including 16 women with endometriosis found a clinically significant reduction in overall pain score at 12 months' follow-up associated with diagnostic laparoscopy compared with excision. *Pelvic pain score at 6 months* **Moderate quality evidence** from 1 study including 39 women with endometriosis found no clinically significant difference in pelvic pain scores at 6 months associated with excision compared with diagnostic laparoscopy. *Dysmenorrhoea pain score at 6 months* **Moderate quality evidence** from 1 study including 39 women with endometriosis found that there was no clinically significant difference in dysmenorrhoea pain score at 6 months associated with excision compared with diagnostic laparoscopy. *Dyspareunia pain score at 6 months* **Moderate quality evidence** from 1 study including 39 women with endometriosis found that there was no clinically significant difference in dyspareunia pain score at 6 months associated with excision compared with diagnostic laparoscopy. *Health-related quality of life*

Content	Description
	Low quality evidence from 1 study including 39 women with endometriosis reported that there was no clinically significant difference in the mean EQ-5D index summary score at 6-month follow -up in the excision groups compared with the diagnostic laparoscopy group. Moderate quality evidence from the same study reported a clinically significant increase in the mean EQ-5D VAS summary score at 6 months associated with excision compared with diagnostic laparoscopy, but no clinically significant difference in the mean SF-12 physical and mental component scores at 6-month follow-up associated with excision compared with diagnostic laparoscopy. **Excisional surgery versus ablative surgery for endometriosis** *Pain scores (improvement from baseline in VAS scores at 12 months)* **Low to very low quality evidence** from 1 randomised controlled trial comprising 103 women with endometriosis showed similar improvement in pain score in the laparoscopic excision and laparoscopic ablation groups for global pain as well as pelvic pain and dyspareunia at 12 months follow-up. One study reported the reduction in VAS score at 5-year follow-up, however, the clinical significance of reported outcomes could not be calculated. *Unintended effects of treatment (improvement from baseline in VAS score at 12 months follow up)* **Moderate to low quality evidence** from 1 randomised controlled trial comprising 103 women with endometriosis showed no clinically significant differences between the 2 treatments in nausea, vomiting and bloating at 12 months follow-up. **Endometrioma** <u>Excisional surgery versus ablative surgery for endometrioma</u> *Recurrence of pelvic pain* **Moderate to low quality evidence** from 2 randomised controlled trials with a total of 104 women with endometriosis showed clinically significant lower rates of recurrence of dysmenorrhoea and non-menstrual pelvic pain associated with laparoscopic excision when compared to laparoscopic ablation of endometrioma. *Pregnancy rate after surgical treatment* **Moderate quality evidence** from 3 randomised controlled trials with a total of 138 women with endometriosis showed higher rates of pregnancy associated with laparoscopic excision compared to laparoscopic ablation after surgical treatment of endometrioma, but there is some uncertainty around this finding which makes judgment of clinical benefit unclear. *Recurrence of endometrioma (at 12 months and at 60 months)* **High quality evidence** from 4 randomised controlled trials with a total of 258 women with endometriosis showed lower rates of recurrence of endometrioma associated with laparoscopic excision when compared to laparoscopic ablation at 12 months follow up. However, this result did not reach clinical significance. Low quality evidence from 1 randomised controlled trial comprising 74 women with endometriosis showed similar rates of recurrence of endometrioma in the laparoscopic excision and laparoscopic ablation groups at 60 months follow-up. *Reoperation after surgical treatment (up to 60 months)* **Very low quality evidence** from 2 randomised controlled trials comprising together of 174 women with endometriosis showed higher rates of reoperations associated with laparoscopic excision when compared to laparoscopic ablation up to 60 months follow up. However, this result did not reach clinical significance.
Recommendations	**40.** Ask women with suspected or confirmed endometriosis about their symptoms, preferences and priorities with respect to pain and fertility, to guide surgical decision-making. **41.** Discuss surgical management options with women with suspected or confirmed endometriosis. Discussions may include: • what a laparoscopy involves • that laparoscopy may include surgical treatment (with prior patient consent) • how laparoscopic surgery could affect endometriosis symptoms • the possible benefits and risks of laparoscopic surgery • the possible need for further surgery (for example, for recurrent endometriosis or if complications arise) • the possible need for further planned surgery for deep endometriosis involving the bowel, bladder or ureter. **42.** Perform surgery for endometriosis laparoscopically unless there are contraindications. **43.** During a laparoscopy to diagnose endometriosis, consider laparoscopic treatment of the following, if present: • peritoneal endometriosis not involving the bowel, bladder or ureter • uncomplicated ovarian endometriomas. **44.** As an adjunct to surgery for deep endometriosis involving the bowel, bladder or ureter, consider 3 months of GnRH agonists[80] before surgery. **45.** Consider excision rather than ablation to treat endometriomas, taking into account the woman's desire for fertility and her ovarian reserve. Also see ovarian reserve testing in the NICE guideline on fertility problems.
Combinations of surgery plus hormonal treatments	
Review question	What is the effectiveness of hormonal treatment before or after surgery for treatment of endometriosis?
Interventions in scope	Any hormonal medical treatment administered before, after or both before + after any surgical treatment

[80] At the time of publication (September 2017), not all gonadotrophin-releasing hormone agonists have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

Content	Description
Critical outcomes	Pain relief, HRQoL, adverse events (specifically withdrawal due to adverse events)
GRADE rating	Very low – moderate
Clinical evidence statements	<u>Pain</u> *Pain recurrence* **Low quality evidence** from 1 trial (n= 53) reported that there is no clinically significant difference between intranasal nafarelin and placebo after surgery for pain recurrence (measured using Andersch and Milsom scale). **Very low quality evidence** from 4 trials (n= 476) found that there is no clinically significant difference between hormonal treatment (triptorelin, goserelin, decapeptyl, letrozole and danazol) and no treatment after surgery for pain recurrence at 12 months. **Very low quality evidence** from 3 trials (n= 312) reported that there is no clinically significant difference between hormonal treatment (leuprolide, goserelin and cyclic combined oral contraceptives) and no treatment after surgery for pain recurrence at 13 to 24 months. **Very low quality evidence** from 1 trial (n=54) reported that there is no clinically significant difference between triptorelin treatment and no treatment after surgery for pain recurrence at 5 years. *Pelvic pain* **Moderate evidence** from 1 trial (n=187) found a clinically significant beneficial effect of hormonal treatments (triptorelin, leuprorelin and oestroprogestin) compared with placebo for pelvic pain (measured using VAS) after surgery although there was low and very low quality evidence of no clinically significant difference between the 2 interventions for dysmenorrhoea and deep dyspareunia. *Dyspareunia* **Low quality evidence** from 1 trial (n=120) found a clinically significant beneficial effect of leuprorelin treatment compared with no treatment for dyspareunia (measured using a questionnaire) after surgery at 12 months although there was low and very quality evidence of no clinically significant difference between the 2 interventions for abdominal pain or dysmenorrhoea. *Dysmenorrhoea* **Moderate quality evidence** from 2 trials (n= 95) found a clinically significant beneficial effect of LGN-IUS treatment compared with no treatment after surgery for dysmenorrhoea at 12 months. *Recurrence of endometriosis* **Very low quality evidence** from 1 trial (n=285) reported that there is no clinically significant difference between leuprolide treatment and no treatment after surgery for recurrence of endometriosis at 5-6 months after starting treatment. **Very low quality evidence** from 3 trials (n=310) reported that there is no clinically significant difference between hormonal treatment (triptorelin, letrozole, leuprolide and danazol) and no treatment after surgery for recurrence of endometriosis at 12 months **Very low quality evidence** from 1 trial (n=45) reported that there is no clinically significant difference between hormonal treatment (danazol or an unspecified GnRH agonist) compared with no treatment after surgery for endometriosis recurrence at 24 months. <u>Recurrence of endometrioma</u> **Low quality evidence** from 3 trials (n= 463) reported a clinically significant beneficial effect of between hormonal treatment (triptorelin, leuprolide and combined oral contraceptives) and placebo or no treatment after surgery for endometrioma recurrence at 13-36 months. **Very low quality evidence** from 1 trial (n=35) reported that there is no clinically significant difference between triptorelin treatment and no treatment after surgery for endometrioma recurrence at 5 years. <u>Health related quality of life</u> **Very low quality evidence** from 1 trial (n=187) reported that women receiving hormone treatment with GnRH agonist or oestroprogestin (oestradiol plus medroxyprogesterone) and women receiving placebo had improved quality of life (improved scores in all domains of the SF-36 general health survey) at 12 months. *Satisfaction* **Low quality evidence** from 2 trials (n=95) reported no clinically significant difference in patient satisfaction with treatment results when LGN-IUS treatment was compared with no treatment after surgery. <u>Reoperation rates</u> **Very low quality evidence** from 3 trials (n=327) reported that there is no clinically significant difference between hormonal treatment (triptorelin, leuprolide, danazol and oestroprogestin) and placebo or no treatment after surgery on reoperation rates.
Recommendations	**46.** After laparoscopic excision or ablation of endometriosis, consider hormonal treatment (with, for example, the combined oral contraceptive pill)[81], to prolong the benefits of surgery and manage symptoms.

[81] At the time of publication (September 2017), not all hormonal treatments (including not all combined oral contraceptive pills) have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

Content	Description
Hysterectomy	
Review question	What is the effectiveness of hysterectomy with or without oophorectomy, including recurrent and asymptomatic endometriosis, in managing endometriosis?
Interventions in scope	Hysterectomy with or without oophorectomy
Critical outcomes	Pain (measured by Biberoglu and Behrman scale or other scale with identical subscales), pain measured by a VAS, QoL (measured using the SF-36)
GRADE rating	Very low
Clinical evidence statements	**Very low quality evidence** from 1 retrospective cohort study with 97 participants showed that there was no clinically significant difference between the 2 interventions for reoperation free survival up to 7 years. **Very low quality evidence** from 1 retrospective cohort study with 136 participants that after a mean follow-up of 4 years 10 months, there was a lower rate of reoperation after hysterectomy with oophorectomy compared to hysterectomy with ovarian conservation. **Very low quality evidence** from 1 retrospective cohort study with 136 participant that after a mean follow-up of 4 years 10 months, there was a lower rate of pain recurrence after hysterectomy with oophorectomy compared to hysterectomy with ovarian conservation.
Recommendations	**47.** If hysterectomy is indicated (for example, if the woman has adenomyosis or heavy menstrual bleeding that has not responded to other treatments), excise all visible endometriotic lesions at the time of the hysterectomy. **48.** Perform hysterectomy (with or without oophorectomy) laparoscopically when combined with surgical treatment of endometriosis, unless there are contraindications. **49.** For women thinking about having a hysterectomy, discuss: • what a hysterectomy involves and when it may be needed • the possible benefits and risks of hysterectomy • the possible benefits and risks of having oophorectomy at the same time • how a hysterectomy (with or without oophorectomy) could affect endometriosis symptoms • that hysterectomy should be combined with excision of all visible endometriotic lesions • endometriosis recurrence and the possible need for further surgery • the possible benefits and risks of hormone replacement therapy after hysterectomy with oophorectomy (also see the NICE guideline on menopause).

Abbreviations: EQ-5D, 5-dimension EuroQoL; GnRH, gonadotropin releasing hormone; HRQoL, health-related quality of life; LGN-IUS, levonorgestrel-releasing intrauterine device; NICE, National Institute of Health Care Excellence; QoL, quality of life; SF-12, 12-item Short Form Health Survey; SF-36, 36-item Short Form Health Survey; VAS, visual analog scale.

Management strategies to enhance fertility (if fertility is a priority)

Table App 10 NICE 2017 Guideline evidence statements and recommendations: Management strategies if fertility is a priority[82]

Content	Description
Review question	What is the effectiveness of the following ovulation suppression treatments or surgery (or combinations of these) or non-pharmacological treatments for improving spontaneous pregnancy rates in endometriosis, including recurrent and asymptomatic endometriosis: • hormonal medical treatments • surgery • non-pharmacological therapies • combinations of surgery plus hormonal treatment?
Interventions in scope	Hormonal medical treatments Surgical treatments Non-pharmacological treatment
Critical outcomes	Live birth, clinical pregnancy, miscarriage
GRADE rating	"GRADE criteria are not currently applied to NMA evidence, but – based on study quality – the body of the evidence would be no better than moderate quality". *16 included studies were assessed as having low to high risk of bias*
Clinical evidence statements	*Not applicable.* *"The Committee agreed that there are limitations to the approach taken in that it addresses only a limited aspect of fertility management that is relevant to women with endometriosis. The Committee addressed this limitation by highlighting the context of NICE's guideline on fertility problems (CG 156) at the beginning of the recommendations which would safeguard that women with endometriosis would receive the same assessment and management options (such as diagnostic tests including ovarian reserve testing, preoperative tests, surgery and assistive reproductive treatments) that other women would receive."*
Recommendations	"The recommendations in this section should be interpreted within the context of NICE's guideline on fertility problems. The management of endometriosis-related infertility should have multidisciplinary team involvement with input from a fertility specialist. This should include the recommended diagnostic fertility tests or preoperative tests, as well as other recommended fertility treatments such as assisted reproduction that are included in the NICE guideline on fertility problems." **50.** Offer excision or ablation of endometriosis plus adhesiolysis for endometriosis not involving the bowel, bladder or ureter, because this improves the chance of spontaneous pregnancy. **51.** Offer laparoscopic ovarian cystectomy with excision of the cyst wall to women with endometriomas, because this improves the chance of spontaneous pregnancy and reduces recurrence. Take into account the woman's ovarian reserve. (Also see ovarian reserve testing in the NICE guideline on fertility problems.) **52.** Discuss the benefits and risks of laparoscopic surgery as a treatment option for women who have deep endometriosis involving the bowel, bladder or ureter and who are trying to conceive (working with a fertility specialist). Topics to discuss may include: • whether laparoscopic surgery may alter the chance of future pregnancy • the possible impact on ovarian reserve (also see ovarian reserve testing in the NICE guideline on fertility problems) • the possible impact on fertility if complications arise • alternatives to surgery • other fertility factors. **53.** Do not offer hormonal treatment to women with endometriosis who are trying to conceive, because it does not improve spontaneous pregnancy rates.

Abbreviations: NICE, National Institute of Health Care Excellence; NMA, network meta-analysis.

[82] Where the impact of surgical or hormonal treatments on fertility are reviewed, the population was restricted to women with endometriosis who had been unsuccessfully trying to conceive and who did not have assisted reproductive treatment (ART). The outcome considered in the network meta-analysis was spontaneous pregnancy (not assisted by reproductive technology).

Risk of cancer of the reproductive organs

Table App 11 NICE 2017 Guideline evidence statements and recommendations: Endometriosis and cancer

Content	Description
Review question	Do women with endometriosis have an increased risk of cancer of the reproductive organs and do they need to be monitored or referred accordingly?
Interventions in scope	Monitoring regimen: Different monitoring regimens (different test or tools), different intervals of monitoring Referral criteria: referral criteria (history, examination and investigation) for suspected or confirmed endometriosis from primary to secondary care
Critical outcomes	Pain, QoL, effect on daily activities
GRADE rating	*Review of prevalence studies – GRADE not used. 15 identified studies were assessed as having very high to high risk of bias*
Clinical evidence statements	Cervical cancer Three studies with **very high to high risk of bias** with 20,686 to 64,492 women with endometriosis compared with the rest of the Swedish population found the SIRs ranged from 0.64 to 0.72, with variable uncertainty. This would suggest that there is not an increased risk of cervical cancer in women with endometriosis. Cancer in situ of the cervix One study with **moderate risk of bias** with 64,492 women with endometriosis was compared to the rest of the Swedish population and found a reduced SIR of 0.89, with little uncertainty. This would suggest that there is not an increased risk of CIS of the cervix in women with endometriosis. Endometrial cancer Three studies with **very high to high risk of bias** with 20,686 to 63,630 women with endometriosis compared with the rest of the Swedish population found the SIRs ranged from 1.09 to1.19 with variable uncertainty. One study with very high risk of bias with 43,734 women hospitalised with endometriosis compared with the rest of the Danish population found an increased risk of endometrial cancer in the women with endometriosis. The SIR was 2.13 (1.77–2.55). Two studies with **very high to high risk of bias** based in Taiwan, looked at 2,266 and 15,488 women with endometriosis compared with 9,064 and 123,904 women without endometriosis and found an increased HR of 4.05 and 2.83 respectively, with large CIs. The differences between the results of the Swedish and Taiwanese studies could be due to a variety of confounding factors (geographical variations, detection differences, statistical analysis and major confounder adjustment). Overall it is unclear whether there is an increased risk of endometrial cancer in women with endometriosis. Ovarian cancer 14 studies with **very high to high risk of bias** with a population of women with endometriosis ranging from 1,919 to 73,724 and a comparison group population of 5,247 to 235,703 (when reported) suggest an increased risk of ovarian cancer in women with endometriosis. Although the studies vary in size, confounder adjustment, statistical analysis (RR, HR, SIR) and comparison group populations (population wide, matched, infertile, geography), they all indicate an increased risk of ovarian cancer with variable certainty of the size of the risk. Borderline ovarian tumour Two studies with **very high and high risk of bias** compared women with endometriosis (n=2,491, n=3,657) with those without endometriosis (n=99,421, n=5247) in a Danish and subfertile population, respectively. The Danish population study did not demonstrate any clinical evidence of an increased risk of borderline ovarian tumour in those with endometriosis. However, compared with the subfertile population, the women with endometriosis were suggested to have an increased risk of borderline ovarian tumour, the degree of which was uncertain. Overall, it is unclear whether there is an increased risk of borderline ovarian tumour in women with endometriosis. Fallopian tube cancer One study with **very high risk of bias** of 64,492 women with endometriosis who were compared with the Swedish population, demonstrated no clinical evidence of an increased risk of fallopian tube cancer with high uncertainty. Uterine otherwise not specified/uterine cancer Four studies of **very high risk of bias** showed no clinical difference in uterine otherwise not specified/uterine cancer between women with endometriosis (n=1,919–64,492) and women without endometriosis (number in the population was not clearly reported but was up to 99,421), with high uncertainty.
Review question	*No recommendation was made on the risk of cancer of the reproductive organs.* *"The Committee concluded that no recommendations should be made based on the available evidence. The most consistent results were related to a possible small increased risk of ovarian cancer in women with endometriosis compared to women without endometriosis. However, because of evidence limitations and the inability to quantify this risk in absolute terms, the Committee decided against making recommendations after considerable debate.* *They decided this because the potential harms associated with misinterpretation or over-interpretation of any recommendation based on this data would outweigh any benefits conferred by women being specifically informed about this data. This may lead to unnecessary procedures. The Committee agreed that for other types of cancer of reproductive organs the evidence was negative or inconclusive."*

Abbreviations: CI, confidence interval; HR, hazard ratio; QoL, quality of life; RR, relative risk; SIR, standardised incidence ratio.

Appendix B PICO, PPO, PIRD criteria for evidence selection

Signs and symptoms

Table App 12 Detailed criteria for Q1: Signs and symptoms

Question 1	**What are the signs and symptoms of endometriosis?** ***[Prognostic question]***	
Population	People suspected of having endometriosis	***Subgroups of interest:*** • People aged 17 and under • Postmenopausal people • Pregnant people • Site of endometriosis (not specified, ovarian, superficial and deep infiltrating {bladder, peritoneal, recto vaginal}, outside the pelvis)
Prognostic factor	Signs Vaginal (visible endometriosis, severe vaginismus); pelvic (palpable nodules in rectovaginal septum and uterosacral ligaments, fixed or tethered uterus and pelvic mass, tender adnexa, tenderness); rectal (palpable extrinsic pelvic mass); renal (loin tenderness, palpable mass); family history of endometriosis Symptoms Pelvic symptoms (pelvic pain, cyclical/non-cyclical); uterus pain (dysmenorrhoea and abnormal bleeding (prolonged and heavy and inter-menstrual bleeding); bowel (rectal bleeding, dyschezia, bloating, constipation and diarrhoea); bladder (bladder pain or irritability, blood in the urine); vaginal pain (painful sex [dyspareunia], pain when using tampons); referred pain (back, leg, thigh, hip); infertility; fatigue; psychological effects (isolation, depression/anxiety, low self-esteem, low mood, poor body image, loss of libido)	
Outcomes	***Critical:*** • Confirmed diagnosis of endometriosis at F/U • Severity of endometriosis • Referral to diagnostic services	***Important:*** • Predictive value of sign or symptom • Accuracy of sign or symptom if used in the diagnosis of endometriosis
Study types	• Systematic reviews • Prospective and retrospective comparative cohort studies • Prospective and retrospective comparative observational studies	***Exclusions:*** • Non-comparative studies
Search date restrictions	• December 2016 onwards • 2009 onwards for subgroups of interest: people with endometriosis outside the pelvis; postmenopausal people; pregnant people	
Bibliographic databases	• Medline • EMBASE	
Other limits	• English-language only • Human studies only	
Additional information	• Isolate papers addressing Aboriginal and Torres Strait Islander populations for consideration by EEWG. • Isolate papers addressing rural and remote populations/settings for consideration by EEWG. • Preferential inclusion of studies using adjusted multivariable analysis (uncontaminated by baseline differences) • Important confounders: age and hormonal contraception	
Original NICE question	What are the symptoms and signs of endometriosis? How and when should women with endometriosis be monitored and referred for the following symptoms or condition progression and complications: pelvic pain disrupting daily activities; cyclical bowel pain; cyclical voiding pain?	
Changes made to NICE criteria	Added the following subgroups: • People with endometriosis occurring outside the pelvis • Postmenopausal people with endometriosis • Pregnant people with endometriosis Removed the following study types: • RCTs (not appropriate for a prognostic question)	

Abbreviations: EEWG, Endometriosis Expert Working Group; F/U, follow up; NICE, National Institute for Health and Care Excellence; RCT, randomised controlled trial.

Information and support

Table App 13 Detailed criteria for Q2a: Information and support

Question 2a	**What information and support do people with endometriosis and their families find helpful?** ***[Intervention question]***	
Population	People with endometriosis (including recurrent endometriosis) or suspected endometriosis, of any stage or severity, and their partners and family ***Exclusions:*** • Studies with indirect populations, such as people with dysmenorrhoea or people with non-confirmed pelvic pain • People with chronic pelvic pain which was known to be due to causes other than endometriosis • People suspected based solely on a CA-125 test with no other contributing factor	***Subgroups of interest:*** • People aged 17 and under • Postmenopausal people • Pregnant people • Site of endometriosis (not specified, ovarian, superficial and deep infiltrating {bladder, peritoneal, recto vaginal}, outside the pelvis)
Intervention	• Support groups • Volunteer supporters • Helplines • Methods of information provision (tools to facilitate): verbal, written, online (and online networks), apps; in groups (peer groups) online or face or face to face, 1:1 advocacy support, online health forum	
Comparator	• Additional information and support with no comparator • Additional information and support vs. usual care	
Outcomes	***Critical:*** • QoL[83] • Psychological wellbeing • Participant wellbeing	***Important:*** • Improved decision-making
Study types	• Systematic reviews of RCTs • Systematic reviews of qualitative studies • RCTs • Comparative cohort studies • Qualitative studies • Cross-sectional studies	
Search date restrictions	• December 2016 onwards • 2009 onwards for subgroups of interest: people with endometriosis outside the pelvis; postmenopausal people; pregnant people	
Bibliographic databases	• Medline • EMBASE • PsychINFO	
Other limits	• English-language only • Human studies only	
Additional information	• Isolate papers addressing Aboriginal and Torres Strait Islander populations for consideration by EEWG. • Isolate papers addressing rural and remote populations/settings for consideration by EEWG. • Capture papers addressing people receiving information through an interpreter.	
Original NICE question	What information and support do women with endometriosis and their families and carers need?	
Changes made to NICE criteria	Added the following subgroups: • People with endometriosis occurring outside the pelvis • Postmenopausal people with endometriosis • Pregnant people with endometriosis	

Abbreviations: CA, cancer antigen; EEWG, Endometriosis Expert Working Group; NICE, National Institute for Health and Care Excellence; QoL, quality of life; RCT, randomised controlled trial.

[83] Measured using a validated scale, for example the SF-36.

Timing of diagnosis and intervention

Table App 14 Detailed criteria for Q3: Timing

Question 3	**In people with suspected endometriosis, is early diagnosis and intervention beneficial?** ***[Prognostic question]***	
Population	People with endometriosis or suspected endometriosis, of any stage or severity ***Exclusions:*** • Studies with indirect populations, such as people with dysmenorrhoea or people with non-confirmed pelvic pain • People with chronic pelvic pain which was known to be due to causes other than endometriosis • People suspected based solely on a CA-125 test with no other contributing factor	***Subgroups of interest:*** • People aged 17 and under • People with endometriosis occurring outside the pelvis • Postmenopausal people • Pregnant people • Type of treatment (surgical or medical) • Severity
Prognostic factor	Duration of symptoms before laparoscopy and treatment	
Outcomes	***Critical*:** • Pain[84] • QoL[85] • Effect on daily activities[86]	***Important*:** • Participant satisfaction with treatment[87]
Study types	• Systematic reviews • Comparative cohort studies • Case-control studies using multivariable adjustment	***Exclusions:*** • Non-comparative studies
Search date restrictions	• December 2016 onwards • 2009 onwards for subgroups of interest: people with endometriosis outside the pelvis; postmenopausal people; pregnant people	
Bibliographic databases	• Medline • EMBASE	
Other limits	• English-language only • Human studies only	
Additional information	• Isolate papers addressing Aboriginal and Torres Strait Islander populations for consideration by EEWG. • Isolate papers addressing rural and remote populations/settings for consideration by EEWG. • Important confounders: severity and type of pain, type of treatment, age, severity and BMI	
Original NICE question	Is there an association between duration of symptoms before laparoscopy and /or treatment and treatment outcomes	
Changes made to NICE criteria	Added the following subgroups: • People with endometriosis occurring outside the pelvis • Postmenopausal people with endometriosis • Pregnant people with endometriosis Change in question type: • From intervention question to prognostic question	

Abbreviations: BMI, body mass index; CA, cancer antigen; EEWG, Endometriosis Expert Working Group; QoL, quality of life; RCT, randomised controlled trial; SF-36, 36-item Short Form Health Survey; VAS, visual analog scale.

[84] Measured either by VAS, other validated scales, or as a dichotomous outcome, for example improved or not improved.
[85] Measured using a validated scale, for example the SF-36.
[86] Measured as proportion of people who reported activity restriction.
[87] Measured as proportion of people who reported improvements and satisfaction with their treatment.

Diagnosis

Endometriosis

Table App 15 Detailed criteria for Q5a: Diagnosis of endometriosis – Clinical examination, ultrasound, CT scan, MRI, biomarkers, surgical diagnosis

Question 5a	**What is the diagnostic performance of clinical examination, ultrasound, CT scan, MRI, biomarkers, and surgery in diagnosing endometriosis?** ***[Diagnostic question]***	
Population	People with suspected endometriosis (symptomatic or asymptomatic) Symptomatic: dyspareunia (pain on intercourse), deep dyspareunia (pain on entry), dyschezia (pain on bowel actions), rectal bleeding, cyclical bleeding, dysmenorrhoea, painful periods Asymptomatic: people who have an appendicitis removed (or any other abdominal surgery) with the finding of an endometrioma or endometriosis; people who have a scan for other reasons with the finding of an endometrioma or endometriosis; people who have a ureteric obstruction; people presenting with symptoms similar to IBS; infertility investigations that discover endometriosis ***Exclusions:*** • Studies with indirect populations, such as people with dysmenorrhoea or people with non-confirmed pelvic pain	***Subgroups of interest:*** • People aged 17 and under • Postmenopausal people • Pregnant people • Deep endometriosis vs superficial endometriosis • Endometriosis occurring outside the pelvis
Index test	• Clinical examination • Ultrasound (transabdominal, transvaginal, rectal scanning) • CT scan • Pelvic MRI • Biomarkers (e.g. CA-125 [cut-off ≥35U/ml], HE-4, PGP 9.5) • Surgical diagnosis with or without histological confirmation	
Reference standard	Surgical visualisation with histological confirmation	
Diagnosis	Endometriosis	
Outcomes	***Critical:*** • Sensitivity • Specificity • Area under the curve (for continuous outcomes) • QoL[88]	
Study types	• Systematic reviews • RCTs (test and treat trials) • Diagnostic test accuracy studies	***Exclusions:*** • Case-control studies
Search date restrictions	• December 2016 onwards • 2009 onwards for subgroups of interest: people with endometriosis outside the pelvis; postmenopausal people; pregnant people • 2009 onwards for new index tests: clinical examination, CT scan	
Bibliographic databases	• Medline • EMBASE	
Other limits	• English-language only • Human studies only	
Additional information	• Isolate papers addressing Aboriginal and Torres Strait Islander populations for consideration by EEWG. • Isolate papers addressing rural and remote populations/settings for consideration by EEWG. • Consider methodological changes in practice, scanning techniques and advances in equipment	
Original NICE question	What is the accuracy of the following tests in diagnosing endometriosis: imaging, biomarkers, surgical diagnosis?	

[88] Measured using a validated scale, for example the SF-36.

Question 5a	What is the diagnostic performance of clinical examination, ultrasound, CT scan, MRI, biomarkers, and surgery in diagnosing endometriosis? *[Diagnostic question]*
Changes made to NICE criteria	Added the following subgroups: • People with endometriosis occurring outside the pelvis • Postmenopausal people with endometriosis • Pregnant people with endometriosis Added the following index tests: • Clinical examination • CT scan

Abbreviations: CA, cancer antigen; CT, computed tomography; EEWG, Endometriosis Expert Working Group; HE-4, human epididymis protein 4; IBS, irritable bowel syndrome; MRI, magnetic resonance imaging; NICE, National Institute for Health and Care Excellence; PGP, Protein Gene Product; QoL, quality of life; RCT, randomised controlled trial; SF-36, 36-item Short Form Health Survey.

Adenomyosis

Table App 16 Detailed criteria for Q5b: Diagnosis of adenomyosis – Ultrasound, MRI

Question 5b	What is the diagnostic performance of ultrasound and MRI in diagnosing adenomyosis? *[Diagnostic and intervention question]*	
Population	People with suspected adenomyosis (symptomatic or asymptomatic) ***Exclusions:*** • Studies with indirect populations, such as people with dysmenorrhoea or people with non-confirmed pelvic pain	***Subgroups of interest:*** • People aged 17 and under • Postmenopausal people • Pregnant people • People with a combination of adenomyosis and endometriosis
Index test	• Ultrasound • Pelvic MRI	
Reference standard	Histological confirmation at surgery	
Diagnosis	Adenomyosis	
Outcomes	***Critical:*** • Sensitivity • Specificity • Area under the curve (for continuous outcomes) • QoL[89]	
Study types	• Systematic reviews • RCTs (test and treat trials) • Diagnostic test accuracy studies	***Exclusions:*** • Case-control studies
Search date restrictions	• 2009 onwards	
Bibliographic databases	• Medline • EMBASE	
Other limits	• English-language only • Human studies only	
Additional information	• Isolate papers addressing Aboriginal and Torres Strait Islander populations for consideration by EEWG. • Isolate papers addressing rural and remote populations/settings for consideration by EEWG. • Consider methodological changes in practice, scanning techniques and advances in equipment	
Original NICE question	This is a new question	
Changes made to NICE criteria	-	

Abbreviations: CA, cancer antigen; CT, computed tomography; EEWG, Endometriosis Expert Working Group; HE-4, human epididymis protein 4; IBS, irritable bowel syndrome; MRI, magnetic resonance imaging; NICE, National Institute for Health and Care Excellence; PGP, Protein Gene Product; QoL, quality of life; RCT, randomised controlled trial; SF-36, 36-item Short Form Health Survey.

[89] Measured using a validated scale, for example the SF-36.

Systems that can guide treatment

Table App 17 Detailed criteria for Q6: Systems that can guide treatment

Question 6	**Do staging systems to guide treatment in people with endometriosis improve patient outcomes?** ***[Intervention question]***	
Population	People with endometriosis (including recurrent endometriosis) of any stage or severity ***Exclusions:*** • Studies with indirect populations, such as people with dysmenorrhoea or people with non-confirmed pelvic pain • People with chronic pelvic pain which was known to be due to causes other than endometriosis • People suspected based solely on a CA-125 test with no other contributing factor • Studies with mixed populations of people with pelvic pain of which < 66% have a confirmed diagnosis of endometriosis	***Subgroups of interest:*** • People aged 17 and under • Postmenopausal people • Pregnant people • Time since diagnosis • Types of pain (cyclical vs non-cyclical, period-like, sharp, dyschezia, painful intercourse, chronic pelvic pain) • Site of endometriosis (not specified, ovarian, superficial and deep infiltrating {bladder, peritoneal, recto vaginal}, outside the pelvis)
Intervention	Systems that grade the overall stage of disease Systems that are specific to fertility Examples: • Revised American Society for Reproductive Medicine (rASRM) staging system • Revised American Fertility Society classification system (rAFS) • Enzian (for staging of deep infiltrating endometriosis only) • Enzian plus rASRM • Endometriosis Fertility Index (EFI) • Surgical staging	***Exclusions:*** • Non-validated scales
Comparator	Usual care (i.e. no staging system)	
Outcomes	***Critical:*** • Pain[90] • QoL[91] • Effect on daily activities[92]	***Important:*** • Accuracy measures (sensitivity / specificity) related to a particular cut-off and outcomes • Prognostic measures (staging as predictors of severity of endometriosis in relation to treatment and patient reported outcomes) • Pregnancy rate / fertility • Unintended effects from treatment (incidence and duration of total side-effects, and type of side-effects) • Participant satisfaction with treatment[93]
Study types	• Systematic reviews • RCTs • Comparative cohort studies • Non-comparative cohort studies	
Search date restrictions	• December 2016 onwards • 2009 onwards for subgroups of interest: people with endometriosis outside the pelvis; postmenopausal people; pregnant people	
Bibliographic databases	• Medline • EMBASE	
Other limits	• English-language only • Human studies only	
Additional information	• Isolate papers addressing Aboriginal and Torres Strait Islander populations for consideration by EEWG. • Isolate papers addressing rural and remote populations/settings for consideration by EEWG.	

[90] Measured either by VAS, other validated scales, or as a dichotomous outcome, for example improved or not improved.
[91] Measured using a validated scale, for example the SF-36.
[92] Measured as proportion of people who reported activity restriction.
[93] Measured as proportion of people who reported improvements and satisfaction with their treatment.

Question 6	**Do staging systems to guide treatment in people with endometriosis improve patient outcomes?** ***[Intervention question]***
Original NICE question	What is the effectiveness of using endometriosis-staging systems to guide treatment of endometriosis?
Changes made to NICE criteria	Added the following subgroups: • People with endometriosis occurring outside the pelvis • Postmenopausal people with endometriosis • Pregnant people with endometriosis

Abbreviations: CA, cancer antigen; EEWG, Endometriosis Expert Working Group; NICE, National Institute for Health and Care Excellence; QoL, quality of life; RCT, randomised controlled trial; SF-36, 36-item Short Form Health Survey; VAS, visual analogue scale.

Treatment

Pharmacological management – Analgesics

Table App 18 Detailed criteria for Q7a: Pharmacological management – Analgesics

Question 7a	**In people with endometriosis or adenomyosis, are analgesics effective for managing endometriosis- or adenomyosis- associated pain?** ***[Intervention question]***	
Population	• People with endometriosis (including recurrent endometriosis) or suspected endometriosis, of any stage or severity • People with adenomyosis or suspected adenomyosis, of any stage or severity ***Exclusions:*** • Studies with indirect populations, such as people with dysmenorrhoea or people with non-confirmed pelvic pain • People with chronic pelvic pain which was known to be due to causes other than endometriosis or adenomyosis	***Subgroups of interest:*** • People aged 17 and under • Postmenopausal people • Pregnant people • Type of diagnosis of endometriosis (e.g. endometrioma; endometriosis occurring outside the pelvis) • Type of NSAIDs
Intervention	• NSAIDs of any type and administered at any dose, frequency, treatment duration, or by any type of administration • Non-opioid analgesics (paracetamol) • NSAIDs and COX-2 inhibitors (diclofenac, ibuprofen, naproxen, celecoxib, mefenamic acid, etoricoxib, indomethacin, tolfenamic acid, aspirin [in doses greater than 600 mg]) • Compound analgesics (co-codamol, co-codaprin, co-dydramol) • Opioid analgesics (codeine, dihydrocodeine, tramadol, buprenorphine) • Medicinal cannabis (medicinal marijuana)	
Comparator	• Analgesic vs no treatment / usual care • Analgesic vs placebo • Analgesic A vs Analgesic B • Analgesic vs other pain management drug	
Outcomes	***Critical:*** • Pain relief[94] • QoL[95] • Effect on daily activities[96]	***Important:*** • Unintended effects from treatment (incidence and duration of total side-effects, and type of side-effects) • Requirements for additional medication[97] • Participant satisfaction with treatment[98]
Study types	• Systematic reviews of RCTs • RCTs • Comparative cohort studies	***Exclusions:*** • Non-comparative studies

[94] Measured either by VAS, other validated scales, or as a dichotomous outcome, for example improved or not improved.
[95] Measured using a validated scale, for example the SF-36.
[96] Measured as proportion of people who reported activity restriction.
[97] Measured as proportion of people requiring analgesics (not NSAIDs) additional to their assigned treatment.
[98] Measured as proportion of people who reported improvements and satisfaction with their treatment).

Question 7a	In people with endometriosis or adenomyosis, are analgesics effective for managing endometriosis- or adenomyosis- associated pain? *[Intervention question]*
Search date restrictions	• December 2016 onwards • 2009 onwards for population of interest: people with adenomyosis • 2009 onwards for subgroups of interest: people with endometriosis outside the pelvis; postmenopausal people; pregnant people • 2009 onwards for new interventions
Bibliographic databases	• Medline • EMBASE
Other limits	• English-language only • Human studies only
Additional information	• Isolate papers addressing Aboriginal and Torres Strait Islander populations for consideration by EEWG. • Isolate papers addressing rural and remote populations/settings for consideration by EEWG.
Original NICE question	What is the effectiveness of analgesics for reducing pain in women with endometriosis, including recurrent and asymptomatic endometriosis?
Changes made to NICE criteria	Added the following populations: • People with adenomyosis Added the following subgroups: • People with endometriosis occurring outside the pelvis • Postmenopausal people with endometriosis • Pregnant people with endometriosis Added the following intervention: • Medicinal cannabis Removed the following 'important' outcomes: • Absence from work or school • Number of people requiring more intensive treatment, and length of follow-up

Abbreviations: COX, cyclooxygenase; EEWG, Endometriosis Expert Working Group; NICE, National Institute for Health and Care Excellence; NSAID, non-steroidal anti-inflammatory drug; QoL, quality of life; RCT, randomised control trial; SF-36, 36-item Short Form Health Survey; VAS, visual analog scale.

Pharmacological management – Neuromodulators

Table App 19 Detailed criteria for Q7b: Pharmacological management – Neuromodulators

Question 7b	In people with endometriosis or adenomyosis, are neuromodulators effective for managing endometriosis- or adenomyosis- associated pain? *[Intervention question]*	
Population	• People with endometriosis (including recurrent or asymptomatic endometriosis) or suspected endometriosis, of any stage or severity • People with adenomyosis or suspected adenomyosis, of any stage or severity ***Exclusions:*** • Studies with indirect populations, such as people with dysmenorrhoea or people with non-confirmed pelvic pain • People with chronic pelvic pain which was known to be due to causes other than endometriosis or adenomyosis • People suspected based solely on a CA-125 test with no other contributing factor • Studies with mixed populations of people with pelvic pain of which < 66% have a confirmed diagnosis of endometriosis	***Subgroups of interest:*** • People aged 17 and under • Postmenopausal people • Pregnant people • Symptomatic or asymptomatic • Types of pain (cyclical vs non-cyclical, period-like, sharp, dyschezia, painful intercourse, chronic pelvic pain) • Type of diagnosis of endometriosis (e.g. endometrioma; endometriosis occurring outside the pelvis)

Question 7b	In people with endometriosis or adenomyosis, are neuromodulators effective for managing endometriosis- or adenomyosis- associated pain? *[Intervention question]*	
Intervention	• Neuromodulators (neuropathic analgesia) of any type and administered at any dose, frequency, treatment duration, or by any type of administration • Tricyclics (amitriptyline, nortriptyline) • SNRIs (duloxetine, mirtazapine, venlafaxine) • Local anaesthetics (lidocaine – topical and infusion) • Capsaicin patches • NMDA antagonist (ketamine) • Anticonvulsants (gabapentin, pregabalin, tiagabine, carbamazepine, phenytoin, valproate topiramate) • Nerve blocks	***Exclusions:*** • nerve ablation
Comparator	• Neuromodulators vs no treatment / usual care • Neuromodulators vs placebo • Neuromodulators A vs Neuro-modulators B • Neuromodulators vs other pain management drug • Neuromodulators vs hormonal treatment • Neuromodulators vs surgical treatment	
Outcomes	***Critical:*** • Pain relief • QoL[99] • Effect on daily activities[100]	***Important:*** • Rate of success (disease recurrence and subsequent reoperation rate) • Unintended effects from treatment (side effects and complications) • Participant satisfaction with treatment • Analgesic use
Study types	• Systematic reviews of RCTs • RCTs • Comparative cohort studies	***Exclusions:*** • Non-comparative studies •
Search date restrictions	• December 2016 onwards • 2009 onwards for population of interest: people with adenomyosis • 2009 onwards for subgroups of interest: people with endometriosis outside the pelvis; postmenopausal people; pregnant people	
Bibliographic databases	• Medline • EMBASE	
Other limits	• English-language only • Human studies only	
Additional information	• Isolate papers addressing Aboriginal and Torres Strait Islander populations for consideration by EEWG. • Isolate papers addressing rural and remote populations/settings for consideration by EEWG. • Stratify results by type/class of neuromodulator, dosage and route of administration	
Original NICE question	What is the effectiveness of neuromodulators for treating endometriosis, including recurrent and asymptomatic endometriosis?	
Changes made to NICE criteria	Added the following populations: • People with adenomyosis Added the following subgroups: • People with endometriosis occurring outside the pelvis • Postmenopausal people with endometriosis • Pregnant people with endometriosis	

Abbreviations: CA, cancer antigen; EEWG, Endometriosis Expert Working Group; NICE, National Institute for Health and Care Excellence; NMDA, N-methyl-D-aspartate; QoL, quality of life; RCT, randomised controlled trial; SF-36, 36-item Short Form Health Survey; SNRI, serotonin and norepinephrine reuptake inhibitors.

[99] Measured using a validated scale, for example the SF-36.
[100] Measured as proportion of people who reported activity restriction which could include; absence from work and school

Pharmacological management – Hormonal medical treatments

Table App 20 Detailed criteria for Q7c: Pharmacological management – Hormonal medical treatments

Question 7c	**In people with endometriosis or adenomyosis, what is the effect of hormonal medical treatments on patient outcomes?** ***[Intervention question]***	
Population	• People with endometriosis (including recurrent or asymptomatic endometriosis) or suspected endometriosis, of any stage or severity • People with adenomyosis or suspected adenomyosis, of any stage or severity ***Exclusions:*** • Studies with indirect populations, such as people with dysmenorrhoea or people with non-confirmed pelvic pain • People with chronic pelvic pain which was known to be due to causes other than endometriosis or adenomyosis • Use of hormonal therapies (excluding depot medroxyprogesterone) in the previous 1 month • Use of depot medroxyprogesterone in the previous 6 months • People suspected based solely on a CA-125 test with no other contributing factor	***Subgroups of interest:*** • People aged 17 and under • Postmenopausal people • Pregnant people • Type of diagnosis of endometriosis (e.g. endometrioma; endometriosis occurring outside the pelvis) • Types of pain • Symptomatic or asymptomatic
Intervention	• Danazol (high dose 400-800 mg/d; low dose 100-400 mg/d) • Gestrinone • Oestrogens (oestradiol oral 1-2 mg/d; conjugated equine oestrogens oral 0.3-1.25 mg/d) • Progestogens (lynestrenol; norethindrone/norethisterone [2.5 mg/d]; gestodene [i.m. 5-10 mg]; desogestrel [oral 75 ug/d]; medroxyprogesterone [low dose oral 15-20 mg/d, high dose oral 20-30 mg/d, i.m. 150 mg/3m, s.c. 104 mg/3 m]; levonorgestrel [20 ug/d released over 5 years]; etonorgestrel [s.c. 68 mg released over 3 years]; dienogest [2 mg/d]) • GnRH agonists (nafarelin [nasal spray – 200 ug/12 h); leuprorelin acetate [depot – 3.75 mg/m]; goserelin [s.c. – 3.6 mg/m]; buserelin [300 ug/8 h]) • Anti-androgens/progestogens (cyproterone acetate [10-12.5 mg/d, only in combination as cOC]) • Aromatase inhibitors (anazstrozole [oral 1 mg/d]; letrozole [oral 2.5 mg/d]) • Selective oestrogen receptor modulators (raloxifene [60 mg/d]) • Selective progestogen receptor modulators (tibolone [oral 2.5 mg/d]) • GnRH antagonists	
Comparator	• All interventions listed above • Surgery (excisional or ablative surgery) with/without interventions listed above • Placebo • No treatment	
Outcomes	***Critical:*** • Pain relief[101] • QoL[102] • Discontinuation of treatment due to adverse effects	***Important:*** • Rate of success (disease recurrence and subsequent reoperation rate) • Participant satisfaction with treatment • Effect on daily activities[103]
Study types	• RCTs (including crossover RCTs)[104]	***Exclusions:*** • Non-randomised studies • Trials with a duration of < 3 months
Search date restrictions	• December 2016 onwards • 2009 onwards for population of interest: people with adenomyosis • 2009 onwards for subgroups of interest: people with endometriosis outside the pelvis; postmenopausal people; pregnant people • 2009 onwards for new interventions: GnRH antagonists, etonorgestrel	

[101] Measured by Biberoglu and Behrman scale or other scale with identical subscales, or by a VAS.
[102] Measured using the SF-36.
[103] Measured as proportion of people who reported activity restriction, which could include absence from work and school.
[104] Both periods of crossover RCTs will be considered if authors have used a suitable paired analysis and if they have tested for carryover effects or have used a suitable washout period.

Question 7c	**In people with endometriosis or adenomyosis, what is the effect of hormonal medical treatments on patient outcomes?** ***[Intervention question]***
Bibliographic databases	• Medline • EMBASE
Other limits	• English-language only • Human studies only
Additional information	• Isolate papers addressing Aboriginal and Torres Strait Islander populations for consideration by EEWG. • Isolate papers addressing rural and remote populations/settings for consideration by EEWG. • The latest time point from each study will be used, up to a maximum duration of 12 months (inclusive) for pain relief and QoL. For discontinuation, maximum duration will depend on whether relative effects change across different study follow-ups.
Original NICE question	What is the effectiveness of the following treatments for pain relief endometriosis, including recurrent and asymptomatic endometriosis: hormonal medical treatments; surgery; non-pharmacological treatments; combinations of surgery plus hormonal treatments?
Changes made to NICE criteria	Added the following populations: • People with adenomyosis Added the following subgroups: • People with endometriosis occurring outside the pelvis • Postmenopausal people with endometriosis • Pregnant people with endometriosis Added the following interventions: • GnRH antagonists • Etonorgestrel Deleted the following interventions: • Triptorelin/dipherelin • Promegestone

Abbreviations: CA, cancer antigen; cOC, combined oral contraceptive; EEWG, Endometriosis Expert Working Group; GnRH, gonadotropin-releasing hormone; i.m., intramuscular; NICE, National Institute for Health and Care Excellence; QoL, quality of life; RCT, randomised control trial; s.c., subcutaneous; SF-36, 36-item Short Form Health Survey; VAS, visual analogue scale.

Alternatives to pharmacological and surgical management

Table App 21 Detailed criteria for Q8: Alternatives to pharmacological and surgical management

Question 8	**In people with endometriosis or adenomyosis, what alternatives to pharmacological and surgical management are effective for managing endometriosis- or adenomyosis- associated pain?** ***[Intervention question]***	
Population	• People with endometriosis (including recurrent endometriosis) or suspected endometriosis, of any stage or severity • People with adenomyosis or suspected adenomyosis, of any stage or severity ***Exclusions:*** • Studies with indirect populations, such as people with dysmenorrhoea or people with non-confirmed pelvic pain • People with chronic pelvic pain which was known to be due to causes other than endometriosis or adenomyosis • Use of hormonal therapies (excluding depot medroxyprogesterone) in the previous 1 month • Use of depot medroxyprogesterone in the previous 6 months • People suspected based solely on a CA-125 test with no other contributing factor	***Subgroups of interest:*** • People aged 17 and under • Postmenopausal people • Pregnant people • Type of diagnosis of endometriosis (e.g. endometrioma; endometriosis occurring outside the pelvis)

Question 8	In people with endometriosis or adenomyosis, what alternatives to pharmacological and surgical management are effective for managing endometriosis- or adenomyosis- associated pain? *[Intervention question]*	
Intervention	• Behavioural/psychological medicine (cognitive behavioural therapy; relaxation techniques' pain management programs; pain management physiotherapy; pain management psychology; expert patient program; hypnosis; psychosexual therapy; biofeedback) • Lifestyle medicine: exercise [e.g. yoga, Pilates, tai chi); meditation; mindfulness; dietary therapies [gluten free; dairy free; vegetarian; FODMAP diet]) • Physical methods: acupuncture; TENS; manual and physical therapy; massage [e.g. shiatsu]; osteopathy; chiropractic treatment; reflexology • Other: dietary supplements; herbal medicine (e.g. Chinese Herbal Medicine); naturopathy; homeopathic therapy; ayurvedic therapies; aromatherapy	
Comparator	• All interventions listed above • Combinations of interventions listed above • Placebo • No treatment	
Outcomes	***Critical:*** • Pain relief[105] • QoL[106] • Discontinuation of treatment due to adverse effects (surgical studies will not be included for this outcome) • Adherence to treatment programs	***Important:*** • Rate of success (disease recurrence and subsequent reoperation rate) • Participant satisfaction with treatment • Effect on daily activities[107]
Study types	• SRs • RCTs (including crossover RCTs)[108]	***Exclusions:*** • Non-randomised studies
Search date restrictions	• December 2016 onwards • 2009 onwards for population of interest: people with adenomyosis • 2009 onwards for subgroups of interest: people with endometriosis outside the pelvis; postmenopausal people; pregnant people • 2009 onwards for new interventions: tai chi, meditation, FODMAP diet, ayurvedic therapies, aromatherapy, dietary supplements	
Bibliographic databases	• Medline • EMBASE	
Other limits	• English-language only • Human studies only	
Additional information	• Isolate papers addressing Aboriginal and Torres Strait Islander populations for consideration by EEWG. • Isolate papers addressing rural and remote populations/settings for consideration by EEWG. • If more than 66% of the sample are within a particular pre-specified strata then the study will be coded as including people with this characteristic. Otherwise this characteristic will be coded as 'mixed'. • The latest time point from each study will be used, up to a maximum duration of 12 months (inclusive) for pain relief and QoL. For discontinuation, maximum duration will depend on whether relative effects change across different study follow-ups.	
Original NICE question	What is the effectiveness of the non-pharmacological treatments for pain relief endometriosis, including recurrent and asymptomatic endometriosis?	

[105] Measured by Biberoglu and Behrman scale or other scale with identical subscales, or by a VAS.
[106] Measured using the SF-36.
[107] Measured as proportion of people who reported activity restriction, which could include absence from work and school.
[108] Both periods of crossover RCTs will be considered if authors have used a suitable paired analysis and if they have tested for carryover effects or have used a suitable washout period.

Question 8	**In people with endometriosis or adenomyosis, what alternatives to pharmacological and surgical management are effective for managing endometriosis- or adenomyosis- associated pain?** ***[Intervention question]***
Changes made to NICE criteria	Added the following populations: • People with adenomyosis Added the following subgroups: • People with endometriosis occurring outside the pelvis • Postmenopausal people with endometriosis • Pregnant people with endometriosis Added the following interventions: • Tai chi • Meditation • FODMAP diet (as a dietary therapy) • Ayurvedic therapies • Aromatherapy • Dietary supplements

Abbreviations: CA, cancer antigen; EEWG, Endometriosis Expert Working Group; NICE, National Institute for Health and Care Excellence; QoL, quality of life; RCT, randomised control trial; TENS, transcutaneous electrical nerve stimulation; VAS, visual analog scale.

Surgical management – Including ablation and excision

Table App 22 Detailed criteria for Q9a: Surgical management – including ablation and excision

Question 9a	**In people with endometriosis or adenomyosis, what is the effect of surgical treatment on patient outcomes?** ***[Intervention question]***	
Population	• People with endometriosis (including recurrent or asymptomatic endometriosis) or suspected endometriosis, of any stage or severity • People with adenomyosis or suspected adenomyosis, of any stage or severity ***Exclusions:*** • Studies with indirect populations, such as people with dysmenorrhoea or people with non-confirmed pelvic pain • People with chronic pelvic pain which was known to be due to causes other than endometriosis or adenomyosis • People suspected based solely on a CA-125 test with no other contributing factor • Studies with mixed populations of people with pelvic pain of which < 66% have a confirmed diagnosis of endometriosis • Use of hormonal therapies (excluding depot medroxyprogesterone) in the previous 1 month	***Subgroups of interest:*** • People aged 17 and under • Postmenopausal people • Pregnant people • Symptomatic or asymptomatic • Types of pain (cyclical vs non-cyclical, period-like, sharp, dyschezia, painful intercourse, chronic pelvic pain) • Type of diagnosis of endometriosis (e.g. endometrioma) • Site of endometriosis (not specified, ovarian, superficial and deep infiltrating {bladder, peritoneal, recto vaginal}, outside the pelvis) • Bowel involvement (shave/skinning, disk, bowel resection)
Intervention	• Ablation • Excision • General techniques (robotic, laparoscopic, open excision, total peritoneal excision) • Specific techniques (laser, diathermy, bipolar and mono polar, ultrasonic energy or a combination [i.e. ultrasonic with bipolar]) • These may also include: ovarian cystectomy, drainage of endometriosis	***Exclusions:*** • Helium coagulation
Comparator	• Surgery compared with diagnostic laparoscopy • Ablation vs excision	

Question 9a	In people with endometriosis or adenomyosis, what is the effect of surgical treatment on patient outcomes? *[Intervention question]*	
Outcomes	***Critical:*** • Pain[109] • QoL[110]	***Important:*** • Rate of success (disease recurrence and subsequent reoperation rate) • Surgical complications • Participant satisfaction with treatment • Effect on daily activities[111]
Study types	• Systematic reviews of RCTs • RCTs	***Exclusions:*** • Non-randomised studies
Search date restrictions	• December 2016 onwards • 2009 onwards for population of interest: people with adenomyosis • 2009 onwards for subgroups of interest: people with endometriosis outside the pelvis; postmenopausal people; pregnant people	
Bibliographic databases	• Medline • EMBASE	
Other limits	• English-language only • Human studies only	
Additional information	• Isolate papers addressing Aboriginal and Torres Strait Islander populations for consideration by EEWG. • Isolate papers addressing rural and remote populations/settings for consideration by EEWG.	
Original NICE question	What is the effectiveness of the following treatments for endometriosis, including recurrent and asymptomatic endometriosis?	
Changes made to NICE criteria	Added the following populations: • People with adenomyosis Added the following subgroups: • People with endometriosis occurring outside the pelvis • Postmenopausal people with endometriosis • Pregnant people with endometriosis Deleted the following 'important' outcome: • Withdrawal due to adverse events	

Abbreviations: CA, cancer antigen; EEWG, Endometriosis Expert Working Group; NICE, National Institute for Health and Care Excellence; QoL, quality of life; RCT, randomised control trial; SF-36, 36-item Short Form Health Survey; VAS, visual analog scale.

[109] Measured by Biberoglu and Behrman scale or other scale with identical subscales, or by a VAS.
[110] Measured using the SF-36.
[111] Measured as proportion of people who reported activity restriction, which could include absence from work and school.

Surgical management – Combination of surgery and hormonal treatment

Table App 23 Detailed criteria for Q9b: Surgical management – Combination of surgery and hormonal treatment

Question 9b	**In people with endometriosis or adenomyosis, do hormonal medical treatments before or after surgery improve patient outcomes?** ***[Intervention question]***	
Population	• People with endometriosis (including recurrent or asymptomatic endometriosis) or suspected endometriosis, of any stage or severity • People with adenomyosis or suspected adenomyosis, of any stage or severity ***Exclusions:*** • Studies with indirect populations, such as people with dysmenorrhoea or people with non-confirmed pelvic pain • People with chronic pelvic pain which was known to be due to causes other than endometriosis or adenomyosis • People suspected based solely on a CA-125 test with no other contributing factor • Studies with mixed populations of people with pelvic pain of which < 66% have a confirmed diagnosis of endometriosis • Use of hormonal therapies (excluding depot medroxyprogesterone) in the previous 1 month	***Subgroups of interest:*** • People aged 17 and under • Postmenopausal people • Pregnant people • Symptomatic or asymptomatic • Types of pain (cyclical vs non-cyclical, period-like, sharp, dyschezia, painful intercourse, chronic pelvic pain) • Type of diagnosis of endometriosis (e.g. endometrioma) • Site of endometriosis (not specified, ovarian, superficial and deep infiltrating {bladder, peritoneal, recto vaginal}, outside the pelvis) • Bowel involvement (shave/skinning, disk, bowel resection)
Intervention	Any hormonal medical treatment administered before, after, or both before and after any surgical treatment	
Comparator	• Hormonal medical treatment before surgery vs no treatment/placebo • Hormonal medical treatment after surgery vs no treatment/placebo • Hormonal medical treatment before vs after surgery • Hormonal medical treatment before and after surgery vs no treatment/usual care	
Outcomes	***Critical:*** • Pain[112] • QoL[113]	***Important:*** • Rate of success (disease recurrence and subsequent reoperation rate) • Surgical complications • Participant satisfaction with treatment • Effect on daily activities[114]
Study types	• Systematic reviews of RCTs • RCTs	***Exclusions:*** • Non-randomised studies • Trials with a duration of < 3 months
Search date restrictions	• December 2016 onwards • 2009 onwards for population of interest: people with adenomyosis • 2009 onwards for subgroups of interest: people with endometriosis outside the pelvis; postmenopausal people; pregnant people	
Bibliographic databases	• Medline • EMBASE	
Other limits	• English-language only • Human studies only	
Additional information	• Isolate papers addressing Aboriginal and Torres Strait Islander populations for consideration by EEWG. • Isolate papers addressing rural and remote populations/settings for consideration by EEWG.	
Original NICE question	What is the effectiveness of pharmacological therapy before or after surgery compared with surgery alone?	

[112] Measured by Biberoglu and Behrman scale or other scale with identical subscales, or by a VAS.
[113] Measured using the SF-36.
[114] Measured as proportion of people who reported activity restriction, which could include absence from work and school.

Question 9b	In people with endometriosis or adenomyosis, do hormonal medical treatments before or after surgery improve patient outcomes? *[Intervention question]*
Changes made to NICE criteria	Added the following populations: • People with adenomyosis Added the following subgroups: • People with endometriosis occurring outside the pelvis • Postmenopausal people with endometriosis • Pregnant people with endometriosis Deleted the following 'important' outcome: • Withdrawal due to adverse events

Abbreviations: CA, cancer antigen; EEWG, Endometriosis Expert Working Group; NICE, National Institute for Health and Care Excellence; QoL, quality of life; RCT, randomised control trial; SF-36, 36-item Short Form Health Survey; VAS, visual analog scale.

Surgical management – Hysterectomy

Table App 24 Detailed criteria for Q9c: Surgical management – Hysterectomy

Question 9c	In people with endometriosis or adenomyosis, what is the effect of hysterectomy on patient outcomes? *[Intervention question]*	
Population	• People with endometriosis (including recurrent or asymptomatic endometriosis), of any stage or severity • People with adenomyosis or suspected adenomyosis, of any stage or severity ***Exclusions:*** • Studies with indirect populations, such as people with dysmenorrhoea or people with non-confirmed pelvic pain	***Subgroups of interest:*** • People aged 17 and under • Postmenopausal people • Postpartum people • Symptomatic or asymptomatic • People with or without cyclic pain • People with a combination of adenomyosis and endometriosis • Hysterectomy with or without excision of endometriosis • Laparoscopy vs laparotomy • Reason for hysterectomy
Intervention	• Hysterectomy without oophorectomy • Hysterectomy with oophorectomy	
Comparator	• No hysterectomy • Hysterectomy without vs. with oophorectomy	
Outcomes	***Critical:*** • Pain[115] • QoL[116]	***Important:*** • Rate of success (disease recurrence and subsequent reoperation rate) • Effect on daily activities[117] • Surgical complications • Participant satisfaction with treatment
Study types	• Systematic reviews of RCTs • RCTs • Prospective and retrospective comparative cohort studies (only if RCTs are unavailable or limited data to inform decision-making)	***Exclusions:*** • Non-comparative studies
Search date restrictions	• December 2016 onwards for hysterectomy without vs. with oophorectomy • 2009 onwards for hysterectomy vs. no hysterectomy • 2009 onwards for population of interest: people with adenomyosis • 2009 onwards for subgroups of interest: people with endometriosis outside the pelvis; postmenopausal people; pregnant people	
Bibliographic databases	• Medline • EMBASE	

[115] Measured by Biberoglu and Behrman scale or other scale with identical subscales, or by a VAS.
[116] Measured using the SF-36.
[117] Measured as proportion of people who reported activity restriction, which could include absence from work and school.

Question 9c	In people with endometriosis or adenomyosis, what is the effect of hysterectomy on patient outcomes? *[Intervention question]*
Other limits	• English-language only • Human studies only
Additional information	• Isolate papers addressing Aboriginal and Torres Strait Islander populations for consideration by EEWG. • Isolate papers addressing rural and remote populations/settings for consideration by EEWG. • Important confounders: age and severity of the condition
Original NICE question	What is the effectiveness of hysterectomy with or without oophorectomy, including recurrent and asymptomatic endometriosis, in managing endometriosis?
Changes made to NICE criteria	Added the following populations: • People with adenomyosis Added the following subgroups: • People with endometriosis occurring outside the pelvis • Postmenopausal people with endometriosis • Postpartum people with endometriosis Added the following comparator: • No hysterectomy

Abbreviations: CA, cancer antigen; EEWG, Endometriosis Expert Working Group; NICE, National Institute for Health and Care Excellence; QoL, quality of life; RCT, randomised control trial; SF-36, 36-item Short Form Health Survey; VAS, visual analog scale.

Management strategies to enhance fertility

Table App 25 Detailed criteria for Q10: Management strategies to enhance fertility

Question 10	In people with endometriosis with and without infertility, what is the effect of hormonal and surgical treatments on fertility? *[Intervention question]*	
Population	• People desiring pregnancy, between menarche and menopause, with endometriosis or suspected endometriosis, of any stage or severity ***Exclusions:*** • Studies with indirect populations, such as people with dysmenorrhoea or people with non-confirmed pelvic pain • People with chronic pelvic pain which was known to be due to causes other than endometriosis or adenomyosis • People suspected based solely on a CA-125 test with no other contributing factor • Use of hormonal therapies (excluding depot medroxyprogesterone) in the previous 1 month • Use of depot medroxyprogesterone in the previous 6 months • People receiving other fertility treatments (e.g. IVF, clomiphene citrate)	***Subgroups of interest:*** • People aged 17 and under • People with infertility • People without infertility • People with deferred fertility due to medical therapy
Intervention	<u>Hormonal medical treatments</u> • Danazol (high dose 400-800 mg/d; low dose 100-400 mg/d) • Gestrinone • Oestrogens (oestradiol oral 1-2 mg/d; conjugated equine oestrogens oral 0.3-1.25 mg/d) • Progestogens (lynestrenol; norethindrone/norethisterone [2.5 mg/d]; gestodene [i.m. 5-10 mg]; desogestrel [oral 75 ug/d]; medroxyprogesterone [low dose oral 15-20 mg/d, high dose oral 20-30 mg/d, i.m. 150 mg/3m, s.c. 104 mg/3m]; levonorgestrel [20 ug/d released over 5 years]; etonorgestrel [s.c. 68 mg released over 3 years]; dienogest [2 mg/d]) • GnRH agonists (nafarelin [nasal spray 200 ug/12 h); leuprorelin acetate [depot 3.75 mg/m]; goserelin [s.c. 3.6 mg/m]; buserelin [300 ug/8 h]) • Anti-androgens/progestogens (cyproterone acetate [10-12.5 mg/d, only in combination as cOC]) • Aromatase inhibitors (anazstrozole [oral 1 mg/d]; letrozole [oral 2.5 mg/d]) • Selective oestrogen receptor modulators (raloxifene [60 mg/d]) • Selective progestogen receptor modulators (tibolone [oral 2.5 mg/d]) • GnRH antagonists	***Exclusions:*** • Helium coagulation

Question 10	**In people with endometriosis with and without infertility, what is the effect of hormonal and surgical treatments on fertility?** ***[Intervention question]***	
	<u>Surgical management</u> • Ablation • Excision • General techniques (robotic, laparoscopic, open excision, total peritoneal excision) • Specific techniques (laser, diathermy, bipolar and mono polar, ultrasonic energy or a combination i.e. ultrasonic with bipolar) • These may also include ovarian cystectomy, drainage of endometriosis	
Comparator	• All interventions listed above • Combinations of interventions listed above • Placebo • No treatment	
Outcomes	***Critical:*** • Live birth • Clinical pregnancy • Miscarriage	***Important:*** • Spontaneous pregnancies
Study types	• Systematic reviews of RCTs • RCTs	***Exclusions:*** • Non-randomised studies • Studies with a duration of < 3 months
Search date restrictions	• December 2016 onwards • 2009 onwards for subgroups of interest: people with endometriosis outside the pelvis; people without infertility • 2009 onwards for new interventions: GnRH antagonists, etonorgestrel	
Bibliographic databases	• Medline • EMBASE	
Other limits	• English-language only • Human studies only	
Additional information	• Isolate papers addressing Aboriginal and Torres Strait Islander populations for consideration by EEWG. • Isolate papers addressing rural and remote populations/settings for consideration by EEWG. • Infertility defined as failure to conceive after ≥12 months unprotected intercourse. • If more than 66% of the sample are within a particular pre-specified strata then the study will be coded as including people with this characteristic. Otherwise this characteristic will be coded as 'mixed'. • The latest time point from each study will be used, up to a maximum duration of 24 months (inclusive).	
Original NICE question	What is the effectiveness of the following ovulation suppression treatments or surgery (or combinations of these) or non-pharmacological treatments for improving spontaneous pregnancy rates in endometriosis, including recurrent and asymptomatic endometriosis: hormonal medical treatments, surgery, non-pharmacological therapies, combinations of surgery plus hormonal treatments?	
Changes made to NICE criteria	Added the following subgroups: • People with endometriosis occurring outside the pelvis • People without infertility • People with deferred fertility due to medical therapy Deleted the following interventions: • Alternatives to pharmacological and surgical management	

Abbreviations: CA, cancer antigen; cOC, combined oral contraceptive; EEWG, Endometriosis Expert Working Group; GnRH, gonadotropin-releasing hormone; i.m., intramuscular; IVF, invitro fertilisation; NICE, National Institute for Health and Care Excellence; QoL, quality of life; RCT, randomised control trial; s.c., subcutaneous.

Follow up in people who are asymptomatic

Table App 26 Detailed criteria for Q11: Follow up

Question 11	**In people with endometriosis who are asymptomatic, do follow-up interventions improve primary patient outcomes?** ***[Intervention question]***	
Population	People who have received surgical or medical treatment for endometriosis and are asymptomatic	***Subgroups of interest:*** • People aged 17 and under • Postmenopausal people • Deep endometriosis vs superficial endometriosis • Endometriosis occurring outside the pelvis
Intervention	• Prophylactic surgery • Second-look surgery • Repeat ultrasound	
Comparator	No follow up interventions	
Outcomes	***Critical:*** • QoL[118] • Unintended effects from treatment (incidence and duration of total side-effects, and type of side-effects) • Rate of success (disease recurrence and subsequent reoperation rate)	
Study types	• Systematic reviews of RCTs • RCTs	***Exclusions:*** • Non-randomised studies
Search date restrictions	• 2009 onwards	
Bibliographic databases	• Medline • EMBASE	
Other limits	• English-language only • Human studies only	
Additional information	• Isolate papers addressing Aboriginal and Torres Strait Islander populations for consideration by EEWG. • Isolate papers addressing rural and remote populations/settings for consideration by EEWG.	
Original NICE question	This is a new question	
Changes made to NICE criteria	-	

Abbreviations: EEWG, Endometriosis Expert Working Group; NICE, National Institute for Health and Care Excellence; QoL, quality of life; RCT, randomised controlled trial; SF-36, 36-item Short Form Health Survey.

[118] Measured using a validated scale, for example the SF-36.

Secondary prevention of endometriosis

Table App 27 Detailed criteria for Q12: Secondary prevention of endometriosis

Question 12	**In people who have received treatment for endometriosis, what interventions prevent the recurrence of endometriosis symptoms and lesions?** ***[Intervention question]***	
Population	People who have received surgical or medical treatment for endometriosis	***Subgroups of interest:*** • People aged 17 and under • Postmenopausal people • Type of diagnosis of endometriosis (e.g. endometrioma) • Site of endometriosis (not specified, ovarian, superficial and deep infiltrating {bladder, peritoneal, recto vaginal}, outside the pelvis)
Intervention	• Prophylactic surgery • Hormonal medical treatments after surgery • Long-term hormonal medical treatment	
Comparator	• No prophylactic surgery • No hormonal medical treatment after surgery • No long-term hormonal medical treatment	
Outcomes	***Critical:*** • Recurrence of pain symptoms • Recurrence of disease	
Study types	• Systematic reviews of RCTs • RCTs	
Search date restrictions	• 2009 onwards	
Bibliographic databases	• Medline • EMBASE	
Other limits	• English-language only • Human studies only	
Additional information	• Isolate papers addressing Aboriginal and Torres Strait Islander populations for consideration by EEWG. • Isolate papers addressing rural and remote populations/settings for consideration by EEWG.	
Original NICE question	This is a new question, but is partly addressed (via recurrence outcomes) in the NICE question relating to combination of surgery plus hormonal medical treatment (Q9b)	
Changes made to NICE criteria	-	

Abbreviations: EEWG, Endometriosis Expert Working Group; NICE, National Institute for Health and Care Excellence; RCT, randomised controlled trial.

Appendix C Search strings

Signs and symptoms

Q1. What are the signs and symptoms of endometriosis?

Table App 28 Signs and symptoms – MEDLINE search strings

No.	Query	Results
1	ENDOMETRIOSIS/ or ADENOMYOSIS/	21,552
2	(endometriosis or endometrioma? or adenomyos#s or adenomyoma? or adenometrit#s or adenomyosit#s or adenomyometrit#s).ti,ab.	25,066
3	or/1-2	28,461
4	exp "SIGNS AND SYMPTOMS"/	2,005,962
5	(sign? or symptom$ or complain$).ti,ab.	1,424,484
6	((clinical or physical or presenting) adj3 (feature? or finding? or factor? or manifest$ or aspect? or characteristic?)).ti,ab.	479,644
7	presentation?.ti,ab.	352,615
8	ABDOMINAL PAIN/ or LOW BACK PAIN/ or PELVIC PAIN/ or PAIN, REFERRED/	45,933
9	(pain$ adj3 (referred or reflective or pelvi? or uterus or uterine or rectal or rectum or bowel? or intestin$ or bladder or urin$ or vagina? or menstrua$ or sex or intercourse or tampon?)).ti,ab.	23,296
10	MENSTRUATION DISTURBANCES/ or DYSMENORRHEA/ or METRORRHAGIA/ or MENORRHAGIA/	15,831
11	UTERINE HEMORRHAGE/	9,398
12	GASTROINTESTINAL HEMORRHAGE/ and RECTUM/	1,578
13	GASTROINTESTINAL HEMORRHAGE/ and RECTAL DISEASES/	918
14	((breakthrough or break through or dysfunction$ or uterine or uterus or vagina? or intermenstrual or inter menstrual or post coital or postcoital or post sex or postsex or after sex or after intercourse or abnormal$ or prolonged or heavy) adj3 (bleed$ or blood or h?emorrhag$)).ti,ab.	34,980
15	(spotting or polymenorrh$ or dysmenorrh$ or metrorrhag$ or menorrhag$).ti,ab.	12,722
16	((rectal or rectum or bowel? or intestin$) adj3 (bleed$ or blood or h?emorrag$)).ti,ab.	11,387
17	((bladder or urin$) adj3 (irritab$ or bleed$ or blood or h?emorrag$)).ti,ab.	28,205
18	CONSTIPATION/ or DIARRHEA/	58,675
19	(constipat$ or dysche$ or diarrh?ea or bloat$).ti,ab.	117,133
20	DYSURIA/ or HEMATURIA/	12,084
21	(dysuri? or h?ematuri?).ti,ab.	23,346
22	DYSPAREUNIA/ or VAGINISMUS/	2,140
23	(dyspareuni? or vaginism$).ti,ab.	3,975
24	INFERTILITY/ or INFERTILITY, FEMALE/	40,164
25	infertil$.ti,ab.	58,054
26	(fertil$ adj3 (problem$ or difficult$)).ti,ab.	1,626
27	FATIGUE/ or ASTHENIA/	28,912
28	SOCIAL ISOLATION/	12,869
29	ANXIETY/ or DEPRESSION/	163,139
30	IRRITABLE MOOD/ or AFFECTIVE SYMPTOMS/	14,201
31	SELF CONCEPT/ or BODY IMAGE/	67,292
32	LIBIDO/	4,657
33	(fatigue? or tired$ or lassitud$ or lonely or loneli$ or anxious or anxiety or depress$).ti,ab.	615,496
34	((low$ or poor or loss or lose or lost) adj3 (mood? or esteem or self esteem or body image or libido)).ti,ab.	7,986
35	exp PALPATION/	8,448
36	((palpa$ or tender$) adj3 (pelvi? or uterus or uterine or rectal or rectum or renal or loin? or adnexa? or abdom$ or rectovaginal septum or uterosacral ligament?)).ti,ab.	5,229
37	((nodule? or mass) adj3 (pelvi? or uterus or uterine or rectal or rectum or renal or loin? or adnexa? or abdom$ or rectovaginal septum or uterosacral ligament?)).ti,ab.	18,527
38	or/4-37	4,417,667

No.	Query	Results
39	exp "SENSITIVITY AND SPECIFICITY"/	562,607
40	(sensitivity or specificity).ti,ab.	989,430
41	((pre test or pretest or post test or posttest) adj probability).ti,ab.	2,635
42	(predictive value$ or PPV or NPV).ti,ab.	109,441
43	likelihood ratio$.ti,ab.	14,641
44	LIKELIHOOD FUNCTIONS/	21,412
45	(ROC curve$ or AUC).ti,ab.	84,175
46	diagnos$.ti.	572,135
47	(diagnos* adj2 (differentia$ or performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.	226,168
48	gold standard.ab.	59,870
49	di.fs.	2,485,177
50	or/39-49	3,960,188
51	and/3,38,50	4,021
52	limit 51 to english language	3,289
53	LETTER/	1,045,124
54	EDITORIAL/	504,187
55	NEWS/	197,462
56	exp HISTORICAL ARTICLE/	391,303
57	ANECDOTES AS TOPIC/	4,732
58	COMMENT/	806,582
59	CASE REPORT/	2,049,145
60	(letter or comment*).ti,ab.	214,838
61	or/53-60	4,284,095
62	ANIMALS/ not HUMANS/	4,593,388
63	exp ANIMALS, LABORATORY/	851,509
64	exp ANIMAL EXPERIMENTATION/	9,172
65	exp MODELS, ANIMAL/	546,834
66	exp RODENTIA/	3,152,264
67	(rat or rats or mouse or mice).ti.	1,304,872
68	or/61-67	9,623,580
69	52 not 68	2,298
70	limit 69 to yr="2016-2019" **[All populations 2016-2019]**	443
71	exp meta-analysis/ or meta-analysis.mp. or metaanalysis.mp. or systematic review.mp. or systematic literature review.mp. or pooled analysis.mp. or (exp review literature as topic/ and systematic.mp.)	265,656
72	Clinical trial/ or Randomized controlled trial/ or Random allocation/ or Double-blind method/ or Cross-over studies/ or (Randomi#ed controlled trial$ or randomi#ed trial$ or rct or random allocation or randomly allocated or allocated randomly or (allocat$ adj3 random) or single blind$ or double blind$ or (((treble or triple) adj blind$) or placebo$)).tw.	1,112,523
73	70 AND 71 **[SRs]**	22
74	70 AND 72 NOT 73 **[RCTs]**	19
75	70 NOT (73 OR 74) **[Other studies]**	402
76	(extrapelvic or extra pelvic or extra genital or extragenital or (outside adj3 pelvi?) or (beyond adj3 pelvi?) or gastrointestin$ or intestin$ or urinary or bowel or colorectal or colon$ or diaphragm$).ti,ab,kw.	1,411,330
77	((endometrio$ adj3 extrapelvic) or (endometrio$ adj3 extra-pelvic) or (endometrio$ adj3 extragenital) or (endometrio$ adj3 extra-genital) or (endometrio$ adj3 gastrointesin$) or (endometrio$ adj3 intesin$) or (endometrio$ adj3 urinary) or (endometrio$ adj3 bowel) or (endometrio$ adj3 colorectal) or (endometrio$ adj3 colon$) or (endometrio$ adj3 diaphragm$) or endometrial implant).ti,ab,kw.	1,261
78	69 AND (77 OR 78)	393
79	limit 78 to yr="2009-2015" **[Extra pelvic population 2009-2015]**	162
80	Pregnancy/ or Pregnant Women/ or pregnan$.ti,ab,kw.	968,169
81	69 AND 80	505
82	limit 82 to yr="2009-2015" **[Pregnant population 2009-2015]**	154

No.	Query	Results
83	menopause/ or postmenopause/ or (menopaus$ or postmenopaus$ or post-menopaus$).ti,ab,kw.	97,817
84	69 AND 83	88
85	limit 84 to yr="2009-2015" [Postmenopausal population 2009-2015]	29

Table App 29 Signs and symptoms – EMBASE search strings

No.	Query	Results
1	ENDOMETRIOSIS/	38,587
2	ADENOMYOSIS/	4,938
3	(endometriosis or endometrioma? or adenomyos#s or adenomyoma? or adenometrit#s or adenomyosit#s or adenomyometrit#s).ti,ab.	38,690
4	or/1-3	46,653
5	exp SYMPTOMATOLOGY/	985,923
6	(sign? or symptom$ or complain$).ti,ab.	2,244,288
7	((clinical or physical or presenting) adj2 (feature? or finding? or factor? or manifest$ or aspect? or characteristic?)).ti,ab.	574,066
8	presentation?.ti,ab.	558,401
9	*ABDOMINAL PAIN/ or *LOWER ABDOMINAL PAIN/	11,551
10	*LOW BACK PAIN/	25,912
11	*CYSTALGIA/	762
12	*PAINFUL DEFECATION/	17
13	*FEMALE GENITAL PAIN/	57
14	*GASTROINTESTINAL PAIN/	61
15	*HIP PAIN/ or *LEG PAIN/ or *LIMB PAIN/	3,004
16	*REFERRED PAIN/	264
17	*URETHRAL PAIN/	33
18	*PELVIC PAIN/	746
19	*URINARY TRACT PAIN/	16
20	*VAGINA PAIN/	78
21	(pain$ adj3 (referred or reflective or pelvi? or uterus or uterine or rectal or rectum or bowel? or intestin$ or bladder or urin$ or vagina? or menstrua$ or sex or intercourse or tampon?)).ti,ab.	39,950
22	*MENSTRUATION DISORDER/	2,787
23	*DYSMENORRHEA/	3,775
24	exp *"MENORRHAGIA AND METRORRHAGIA"/	4,819
25	*UTERUS BLEEDING/	3,779
26	*RECTUM HEMORRHAGE/	1,933
27	*BLADDER BLEEDING/ or *URETHRAL BLEEDING/	221
28	((breakthrough or break through or dysfunction$ or uterine or uterus or vagina? or intermenstrual or inter menstrual or post coital or postcoital or post sex or postsex or after sex or after intercourse or abnormal$ or prolonged or heavy) adj3 (bleed$ or blood or h?emorrhag$)).ti,ab.	55,844
29	(spotting or polymenorrh$ or dysmenorrh$ or metrorrhag$ or menorrhag$).ti,ab.	19,601
30	((rectal or rectum or bowel? or intestin$) adj3 (bleed$ or blood or h?emorrag$)).ti,ab.	19,708
31	((bladder or urin$) adj3 (irritab$ or bleed$ or blood or h?emorrag$)).ti,ab.	45,359
32	*CONSTIPATION/ or *DIARRHEA/	48,096
33	(constipat$ or dysche$ or diarrh?ea or bloat$).ti,ab.	188,690
34	*DYSURIA/ or *HEMATURIA/	8,639
35	(dysuri? or h?ematuri?).ti,ab.	39,103
36	*DYSPAREUNIA/ or *VAGINISM/	1,603
37	(dyspareuni? or vaginism$).ti,ab.	7,919
38	*INFERTILITY/ or *FEMALE INFERTILITY/	32,056
39	infertil$.ti,ab.	86,163

No.	Query	Results
40	(fertil$ adj3 (problem$ or difficult$)).ti,ab.	2,346
41	*FATIGUE/ or *ASTHENIA/	23,674
42	*SOCIAL ISOLATION/	6,009
43	*ANXIETY/	53,751
44	exp *DEPRESSION/	208,314
45	*MOOD CHANGE/	455
46	*IRRITABILITY/	1,774
47	*SELF ESTEEM/	3,903
48	*BODY IMAGE/	8,181
49	*LIBIDO DISORDER/	227
50	(fatigue? or tired$ or lassitud$ or lonely or loneli$ or anxious or anxiety or depress$).ti,ab.	899,931
51	((low$ or poor or loss or lose or lost) adj3 (mood? or esteem or self esteem or body image or libido)).ti,ab.	11,507
52	*PALPATION/	1,662
53	*DIGITAL RECTAL EXAMINATION/	499
54	((palpa$ or tender$) adj2 (pelvi? or uterus or uterine or rectal or rectum or renal or loin? or adnexa? or abdom$ or rectovaginal septum or uterosacral ligament?)).ti,ab.	7,146
55	((nodule? or mass) adj2 (pelvi? or uterus or uterine or rectal or rectum or renal or loin? or adnexa? or abdom$ or rectovaginal septum or uterosacral ligament?)).ti,ab.	24,736
56	or/5-55	4,602,773
57	"SENSITIVITY AND SPECIFICITY"/	340,694
58	(sensitivity or specificity).ti,ab.	1,305,924
59	((pre test or pretest or post test or posttest) adj probability).ti,ab.	4,465
60	(predictive value$ or PPV or NPV).ti,ab.	168,235
61	likelihood ratio$.ti,ab.	20,002
62	STATISTICAL MODEL/	157,446
63	(ROC curve$ or AUC).ti,ab.	144,593
64	diagnos$.ti.	747,862
65	(diagnos* adj2 (differentia$ or performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.	344,053
66	gold standard.ab.	100,092
67	*DIAGNOSTIC ACCURACY/ or DIAGNOSTIC TEST ACCURACY STUDY/	121,525
68	di.fs.	3,181,931
69	or/57-68	5,136,300
70	and/4,56,69	7,268
71	limit 70 to english language	6,305
72	letter.pt. or LETTER/	1,095,134
73	note.pt.	775,811
74	editorial.pt.	634,513
75	CASE REPORT/ or CASE STUDY/	2,577,427
76	(letter or comment*).ti,ab	294,627
77	or/72-76	4,956,648
78	ANIMAL/ not HUMAN/	1,463,804
79	NONHUMAN/	5,982,052
80	exp ANIMAL EXPERIMENT/	2,466,929
81	exp EXPERIMENTAL ANIMAL/	676,270
82	ANIMAL MODEL/	1,275,765
83	exp RODENT/	3,919,821
84	(rat or rats or mouse or mice).ti.	1,640,236
85	or/77-84	13,348,191
86	71 not 85	3,960

No.	Query	Results
87	limit 86 to yr="2016-2019" [All populations 2016-2019]	850
88	meta-analysis/ or meta-analysis.mp. or metaanalysis.mp. or systematic review/ or systematic review.mp. or systematic literature review.mp. or pooled analysis.mp.	435,872
89	clinical trial/ or randomized controlled trial/ or randomization/ or crossover procedure/ or (randomi#ed controlled trial$ or randomi#ed trial$ or rct or (allocat$ adj3 random$) or single blind$ or double blind$ or placebo$).tw.	1,669,203
90	87 AND 88 [SRs]	68
91	87 AND 89 NOT 90 [RCTs]	48
92	87 NOT (90 OR 91) [Other studies]	734
93	(extrapelvic or extra pelvic or extra genital or extragenital or (outside adj3 pelvi?) or (beyond adj3 pelvi?) or gastrointestin$ or intestin$ or urinary or bowel or colorectal or colon$ or diaphragm$).ti,ab,kw.	2,008,129
94	((endometrio$ adj3 extrapelvic) or (endometrio$ adj3 extra-pelvic) or (endometrio$ adj3 extragenital) or (endometrio$ adj3 extra-genital) or (endometrio$ adj3 gastrointesin$) or (endometrio$ adj3 intesin$) or (endometrio$ adj3 urinary) or (endometrio$ adj3 bowel) or (endometrio$ adj3 colorectal) or (endometrio$ adj3 colon$) or (endometrio$ adj3 diaphragm$) or endometrial implant).ti,ab,kw.	2,164
95	86 and (93 or 94)	736
96	limit 95 to yr="2009 - 2015" [Extra pelvic population 2009-2015]	366
97	96 AND 88 [SRs]	17
98	96 AND 89 NOT 97 [RCTs]	19
99	96 NOT (97 OR 98) [Other studies]	330
100	menopause/ or postmenopause/ or (menopaus$ or postmenopaus$ or post-menopaus$).ti,ab,kw.	157,041
101	86 and 100 NOT 96	233
102	limit 101 to yr="2009 - 2015" [Postmenopausal population 2009-2015]	86
103	pregnancy/ or pregnant woman/ or pregnan$.ti,ab,kw.	1,012,430
104	86 and 103 NOT (96 OR 102)	654
105	limit 104 to yr="2009 - 2015" [Pregnant population 2009-2015]	209

Information and support

Q2a. What information and support do people with endometriosis and their families find helpful?

Table App 30 Information and support – MEDLINE search strings

No.	Query	Results
1	ENDOMETRIOSIS/ or ADENOMYOSIS/ or (endometriosis or endometrioma? or adenomyos#s or adenomyoma? or adenometrit#s or adenomyosit#s or adenomyometrit#s).ti,ab.	28,488
2	HEALTH EDUCATION/ or exp CONSUMER HEALTH INFORMATION/ or PATIENT EDUCATION AS TOPIC/ or patient education handout.pt. or guideline.pt. or ((information$ or educat$ or learn$ or train$ or program$ or advi?e$ or instruction$ or teach$ or knowledge or understanding or misunderstanding or communicat$ or involvement or support$ or counsel$) adj3 (pamphlet$ or leaflet$ or booklet$ or manual$ or brochure$ or publication$ or handout$ or website$ or web site$ or web page$ or webpage$ or video$ or dvd$ or online$ or internet$ or app? or application?)).ti,ab.	224,887
3	((helpline? or ((volunt$ or peer$) adj3 support$) or ((information$ or educat$) adj3 (model$ or program$ or need$ or requirement$ or support$ or seek$ or access$ or disseminat$)) or ((verbal$ or written or group or individual$) adj3 (information$ or educat$ or communicat$ or support$ or counsel$))).ti,ab. or (PUBLICATIONS/ or PAMPHLETS/ or POSTERS AS TOPIC/)) and (patient$ or wom#n$ or famil$ or partner? or husband$).ti,ab.	100,999
4	exp COUNSELING/ or DECISION SUPPORT TECHNIQUES/ or SOCIAL SUPPORT/ or COMMUNITY NETWORKS/ or PEER GROUP/	150,061
5	((patient$ or wom#n$ or famil$ or partner? or husband$) adj3 (information$ or educat$ or learn$ or train$ or program$ or advi?e$ or instruct$ or teach$ or knowledge or understanding or misunderstanding or communicat$ or involvement or support$ or counsel$)).ti,ab.	312,514
6	((patient$ or wom#n$ or famil$ or partner? or husband$) adj3 (pamphlet$ or leaflet$ or booklet$ or manual$ or brochure$ or publication$ or handout$ or website$ or web site$ or web page$ or webpage$ or video$ or dvd$ or online$ or internet$ or app? or application?)).ti,ab.	26980
7	SEXUAL DYSFUNCTION, PHYSIOLOGICAL/px	1601
8	DYSPAREUNIA/px	262

No.	Query	Results
9	((relationship$ or sex$ or psychosexual or intercourse or dyspareuni$ or fertility) adj3 (information$ or educat$ or learn$ or train$ or program$ or advi?e$ or instruct$ or teach$ or knowledge or understanding or misunderstanding or communicat$ or involvement or support$ or counsel$)).ti,ab.	72763
10	or/2-9	749552
11	1 and 10	624
12	limit 11 to english language	570
13	12 not ((LETTER/ or EDITORIAL/ or NEWS/ or exp HISTORICAL ARTICLE/ or ANECDOTES AS TOPIC/ or COMMENT/ or CASE REPORT/ or (letter or comment*).ti.) not (RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.))	502
14	13 not ((ANIMALS/ not HUMANS/) or exp ANIMALS, LABORATORY/ or exp ANIMAL EXPERIMENTATION/ or exp MODELS, ANIMAL/ or exp RODENTIA/ or (rat or rats or mouse or mice).ti.)	492
15	limit 14 to yr="2016-2019" **[All populations 2016-2019]**	153
16	limit 14 to yr="2009-2015"	155
17	(extrapelvic or extra pelvic or extra genital or extragenital or (outside adj3 pelvi?) or (beyond adj3 pelvi?) or gastrointestin$ or intestin$ or urinary or bowel or colorectal or colon$ or diaphragm$ or endometrial implant$).ti,ab,kw.	1412857
18	16 and 17 **[Extra pelvic population 2009-2015]**	34
19	menopause/ or postmenopause/ or (menopaus$ or postmenopaus$ or post-menopaus$).ti,ab,kw.	97879
20	(16 and 19) not 18 **[Postmenopausal population 2009-2015]**	4
21	pregnancy/ or pregnant woman/ or pregnan$.ti,ab,kw.	968672
22	(16 and 21) not (18 or 20) **[Pregnant population 2009-2015]**	24

Table App 31 Information and support – EMBASE search strings

No.	Query	Results
1	ENDOMETRIOSIS/ or ADENOMYOSIS/ or (endometriosis or endometrioma? or adenomyos#s or adenomyoma? or adenometrit#s or adenomyosit#s or adenomyometrit#s).ti,ab.	46,665
2	HEALTH EDUCATION/ or CONSUMER HEALTH INFORMATION/ or PATIENT EDUCATION/ or ((information$ or educat$ or learn$ or train$ or program$ or advi?e$ or instruction$ or teach$ or knowledge or understanding or misunderstanding or communicat$ or involvement or support$ or counsel$) adj3 (pamphlet$ or leaflet$ or booklet$ or manual$ or brochure$ or publication$ or handout$ or website$ or web site$ or web page$ or webpage$ or video$ or dvd$ or online$ or internet$ or app? or application?)).ti,ab.	290,725
3	((helpline? or ((volunt$ or peer$) adj3 support$) or ((information$ or educat$) adj3 (model$ or program$ or need$ or requirement$ or support$ or seek$ or access$ or disseminat$)) or ((verbal$ or written or group or individual$) adj3 (information$ or educat$ or communicat$ or support$ or counsel$))).ti,ab. or PUBLICATION/) and (patient$ or wom#n$ or famil$ or partner? or husband$).ti,ab.	180,232
4	exp COUNSELING/ or DECISION SUPPORT SYSTEM/ or SOCIAL SUPPORT/ or PEER GROUP/	286,578
5	((patient$ or wom#n$ or famil$ or partner? or husband$) adj3 (information$ or educat$ or learn$ or train$ or program$ or advi?e$ or instruct$ or teach$ or knowledge or understanding or misunderstanding or communicat$ or involvement or support$ or counsel$)).ti.	64,346
6	((patient$ or wom#n$ or famil$ or partner? or husband$) adj3 (pamphlet$ or leaflet$ or booklet$ or manual$ or brochure$ or publication$ or handout$ or website$ or web site$ or web page$ or webpage$ or video$ or dvd$ or online$ or internet$ or app? or application?)).ti,ab.	45,077
7	(SEXUAL DYSFUNCTION/ or FEMALE SEXUAL DYSFUNCTION/ or DYSPAREUNIA/) and (information$ or educat$ or learn$ or train$ or program$ or advi?e$ or instruct$ or teach$ or knowledge or understanding or misunderstanding or communicat$ or involvement or support$ or counsel$).ti.	1,198
8	((relationship$ or sex$ or psychosexual or intercourse or dyspareuni$ or fertility) adj3 (information$ or educat$ or learn$ or train$ or program$ or advi?e$ or instruct$ or teach$ or knowledge or understanding or misunderstanding or communicat$ or involvement or support$ or counsel$)).ti,ab.	95,253
9	or/2-8	833,334
10	1 and 9	1,112
11	limit 10 to english language	1,058
12	11 not ((letter.pt. or LETTER/ or note.pt. or editorial.pt. or CASE REPORT/ or CASE STUDY/ or (letter or comment*).ti.) not (RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.))	870
13	12 not ((ANIMAL/ not HUMAN/) or NONHUMAN/ or exp ANIMAL EXPERIMENT/ or exp EXPERIMENTAL ANIMAL/ or ANIMAL MODEL/ or exp RODENT/ or (rat or rats or mouse or mice).ti.)	823
14	limit 13 to yr="2016-2019" **[All populations 2016-2019]**	290

No.	Query	Results
15	meta-analysis/ or meta-analysis.mp. or metaanalysis.mp. or systematic review/ or systematic review.mp. or systematic literature review.mp. or pooled analysis.mp.	433,522
16	clinical trial/ or randomized controlled trial/ or randomization/ or crossover procedure/ or (randomi#ed controlled trial$ or randomi#ed trial$ or rct or (allocat$ adj3 random$) or single blind$ or double blind$ or placebo$).tw.	1,671,254
17	14 and 15 **[SRs]**	31
18	(14 and 16) not 17 **[RCTs]**	17
19	14 not (17 or 18) **[Other studies]**	242
20	limit 13 to yr="2009-2015"	371
21	(extrapelvic or extra pelvic or extra genital or extragenital or (outside adj3 pelvi?) or (beyond adj3 pelvi?) or gastrointestin$ or intestin$ or urinary or bowel or colorectal or colon$ or diaphragm$).ti,ab,kw.	2,009,208
22	20 and 21 **[Extra pelvic population 2009-2015]**	89
23	menopause/ or postmenopause/ or (menopaus$ or postmenopaus$ or post-menopaus$).ti,ab,kw.	157,070
24	(20 and 23) not 22 **[Postmenopausal population 2009-2015]**	21
25	pregnancy/ or pregnant woman/ or pregnan$.ti,ab,kw.	1,012,975
26	(13 and 25) not (22 or 24) **[Pregnant population 2009-2015]**	155

Table App 32 Information and support – PsychINFO search strings

No.	Query	Results
1	(endometriosis or endometrioma? or adenomyos#s or adenomyoma? or adenometrit#s or adenomyosit#s or adenomyometrit#s).ti,ab,id.	258
2	exp HEALTH EDUCATION/ or CLIENT EDUCATION/ or ((information$ or educat$ or learn$ or train$ or program$ or advi?e$ or instruction$ or teach$ or knowledge or understanding or misunderstanding or communicat$ or involvement or support$ or counsel$) adj3 (pamphlet$ or leaflet$ or booklet$ or manual$ or brochure$ or publication$ or handout$ or website$ or web site$ or web page$ or webpage$ or video$ or dvd$ or online$ or internet$ or app? or application?)).ti,ab.	68,243
3	((helpline? or ((volunt$ or peer$) adj3 support$) or ((information$ or educat$) adj3 (model$ or program$ or need$ or requirement$ or support$ or seek$ or access$ or disseminat$)) or ((verbal$ or written or group or individual$) adj3 (information$ or educat$ or communicat$ or support$ or counsel$))).ti,ab. or (INFORMATION DISSEMINATION/ or exp READING MATERIALS/)) and (patient$ or wom#n$ or famil$ or partner? or husband$).ti,ab.	48,533
4	exp COUNSELING/ or DECISION SUPPORT SYSTEMS/ or SOCIAL SUPPORT/ or exp SOCIAL NETWORKS/ or PEERS/ or PEER RELATIONS/ or PEER TUTORING/	156,076
5	((patient$ or wom#n$ or famil$ or partner? or husband$) adj3 (information$ or educat$ or learn$ or train$ or program$ or advi?e$ or instruct$ or teach$ or knowledge or understanding or misunderstanding or communicat$ or involvement or support$ or counsel$)).ti,ab.	125,722
6	((patient$ or wom#n$ or famil$ or partner? or husband$) adj3 (pamphlet$ or leaflet$ or booklet$ or manual$ or brochure$ or publication$ or handout$ or website$ or web site$ or web page$ or webpage$ or video$ or dvd$ or online$ or internet$ or app? or application?)).ti,ab.	7,093
7	SEXUAL FUNCTION DISTURBANCES/ or FEMALE SEXUAL DYSFUNCTION/ or DYSPAREUNIA/ or ((relationship$ or sex$ or psychosexual or intercourse or dyspareuni$ or fertility) adj3 (information$ or educat$ or learn$ or train$ or program$ or advi?e$ or instruct$ or teach$ or knowledge or understanding or misunderstanding or communicat$ or involvement or support$ or counsel$)).ti,ab.	88,076
8	or/2-7	418,565
9	1 and 8	43
10	limit 9 to english language	39
11	limit 10 to yr="2016-2019" **[All populations 2016-2019]**	9
12	limit 10 to yr="2009-2015"	17
13	(extrapelvic or extra pelvic or extra genital or extragenital or (outside adj3 pelvi?) or (beyond adj3 pelvi?) or gastrointestin$ or intestin$ or urinary or bowel or colorectal or colon$ or diaphragm$ or endometrial implant$).ti,ab,id.	37,572
14	12 and 13 **[Extra pelvic population 2009-2015]**	1
15	menopause/ or (postmenopaus$ or post-menopaus$ or menopause$).ti,ab,id.	5,919
16	(12 and 15) not 14 **[Postmenopausal population 2009-2015]**	1

No.	Query	Results
17	pregnancy/ or expectant mothers/ or pregnan$.ti,ab,id.	47,616
18	(12 and 17) not (14 or 16) [Pregnant population 2009-2015]	0

Timing of diagnosis and intervention

Q3. In people with suspected endometriosis, is early diagnosis and intervention beneficial?

Table App 33 Timing – MEDLINE search strings

No.	Query	Results
1	ENDOMETRIOSIS/	21,082
2	ADENOMYOSIS/	652
3	(endometriosis or endometrioma? or adenomyos#s or adenomyoma? or adenometrit#s or adenomyosit#s or adenomyometrit#s).ti,ab.	25,066
4	or/1-3	28,461
5	EARLY DIAGNOSIS/	25,063
6	DELAYED DIAGNOSIS/	5,704
7	DIAGNOSTIC ERRORS/	36,825
8	AGE OF ONSET/	36,460
9	TIME-TO-TREATMENT/	5,349
10	AGE DISTRIBUTION/	64,771
11	((disease or endometriosis) adj3 (duration or onset)).ti,ab.	64,880
12	((early or delay$) adj2 (diagnos$ or detect$ or treat$ or surg$)).ti,ab.	256,991
13	((age$ or time or early or delay$ or symptom$) adj2 onset).ti,ab.	120,758
14	time factor$.ti,ab.	1,754
15	or/5-14	554,387
16	4 and 15	867
17	ENDOMETRIOSIS/di, su, th [DIAGNOSIS, SURGERY, THERAPY]	8,344
18	TIME FACTORS/	1,163,244
19	17 and 18	315
20	16 or 19	1,151
21	limit 20 to english language	971
22	LETTER/	1,045,124
23	EDITORIAL/	504,187
24	NEWS/	197,462
25	exp HISTORICAL ARTICLE/	391,303
26	ANECDOTES AS TOPIC/	4,732
27	COMMENT/	806,582
28	CASE REPORT/	2,049,145
29	(letter or comment*).ti.	143,533
30	or/22-29	4,222,045
31	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.	1,199,358
32	30 not 31	4,197,208
33	ANIMALS/ not HUMANS/	4,593,388
34	exp ANIMALS, LABORATORY/	851,509
35	exp ANIMAL EXPERIMENTATION/	9,172
36	exp MODELS, ANIMAL/	546,834
37	exp RODENTIA/	3,152,264
38	(rat or rats or mouse or mice).ti.	1,304,872
39	or/32-38	9,539,775

No.	Query	Results
40	21 not 39	773
41	limit 40 to yr="2016-2019" **[All populations 2016-2019]**	188
42	exp meta-analysis/ or meta-analysis.mp. or metaanalysis.mp. or systematic review.mp. or systematic literature review.mp. or pooled analysis.mp. or (exp review literature as topic/ and systematic.mp.)	265,509
43	Clinical trial/ or Randomized controlled trial/ or Random allocation/ or Double-blind method/ or Cross-over studies/ or (Randomi#ed controlled trial$ or randomi#ed trial$ or rct or random allocation or randomly allocated or allocated randomly or (allocat$ adj3 random) or single blind$ or double blind$ or (((treble or triple) adj blind$) or placebo$)).tw.	1,112,279
44	41 AND 42 **[SRs]**	5
45	41 AND 43 NOT 44 **[RCTs]**	8
46	41 NOT (44 OR 45) **[Other studies]**	175
47	(extrapelvic or extra pelvic or extra genital or extragenital or (outside adj3 pelvi?) or (beyond adj3 pelvi?) or gastrointestin$ or intestin$ or urinary or bowel or colorectal or colon$ or diaphragm$).ti,ab,kw.	1,411,330
48	((endometrio$ adj3 extrapelvic) or (endometrio$ adj3 extra-pelvic) or (endometrio$ adj3 extragenital) or (endometrio$ adj3 extra-genital) or (endometrio$ adj3 gastrointesin$) or (endometrio$ adj3 intesin$) or (endometrio$ adj3 urinary) or (endometrio$ adj3 bowel) or (endometrio$ adj3 colorectal) or (endometrio$ adj3 colon$) or (endometrio$ adj3 diaphragm$) or endometrial implant).ti,ab,kw.	1,261
49	40 AND (47 OR 48)	120
50	limit 49 to yr="2009-2015" **[Extra pelvic population 2009-2015]**	50
51	Pregnancy/ or Pregnant Women/ or pregnan$.ti,ab,kw.	968,169
52	40 AND 51	161
53	limit 52 to yr="2009-2015" **[Pregnant population 2009-2015]**	50
54	menopause/ or postmenopause/ or (menopaus$ or postmenopaus$ or post-menopaus$).ti,ab,kw.	97,817
55	40 AND 54	40
56	limit 55 to yr="2009-2015" **[Postmenopausal population 2009-2015]**	12

Table App 34 Timing – EMBASE search strings

No.	Query	Results
1	*ENDOMETRIOSIS/	25038
2	*ADENOMYOSIS/	2235
3	(endometriosis or endometrioma? or adenomyos#s or adenomyoma? or adenometrit#s or adenomyosit#s or adenomyometrit#s).ti,ab.	38692
4	or/1-3	40543
5	EARLY DIAGNOSIS/	110935
6	DELAYED DIAGNOSIS/	11878
7	DIAGNOSTIC ERRORS/	54566
8	ONSET AGE/	81003
9	TIME TO TREATMENT/	15093
10	AGE DISTRIBUTION/	140146
11	((disease or endometriosis) adj3 (duration or onset)).ti,ab.	126402
12	((early or delay$) adj2 (diagnos$ or detect$ or treat$ or surg$)).ti,ab.	396373
13	((age$ or time or early or delay$ or symptom$) adj2 onset).ti,ab.	190490
14	time factor$.ti,ab.	2829
15	or/5-14	942766
16	4 and 15	1563
17	ENDOMETRIOSIS/di, dt, su [DIAGNOSIS, DRUG THERAPY, SURGERY]	13080
18	TIME/	395963
19	17 and 18	91
20	16 or 19	1653
21	limit 20 to english language	1440
22	letter.pt. or LETTER/	1095150

23	note.pt.	775833
24	editorial.pt.	634526
25	CASE REPORT/ or CASE STUDY/	2578026
26	(letter or comment*).ti.	199098
27	or/22-26	4872495
28	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.	1584110
29	27 not 28	4828629
30	ANIMAL/ not HUMAN/	1463804
31	NONHUMAN/	5982555
32	exp ANIMAL EXPERIMENT/	2467192
33	exp EXPERIMENTAL ANIMAL/	676364
34	ANIMAL MODEL/	1275959
35	exp RODENT/	3919991
36	(rat or rats or mouse or mice).ti.	1640290
37	or/29-36	13230584
38	21 not 37	1100
39	limit 38 to yr="2016-2019" **[All populations 2016-2019]**	296
40	meta-analysis/ or meta-analysis.mp. or metaanalysis.mp. or systematic review/ or systematic review.mp. or systematic literature review.mp. or pooled analysis.mp.	433068
41	clinical trial/ or randomized controlled trial/ or randomization/ or crossover procedure/ or (randomi#ed controlled trial$ or randomi#ed trial$ or rct or (allocat$ adj3 random$) or single blind$ or double blind$ or placebo$).tw.	1670741
42	39 AND 40 **[SRs]**	18
43	39 AND 41 NOT 42 **[RCTs]**	7
44	39 NOT (42 OR 43) **[Other studies]**	271
45	(extrapelvic or extra pelvic or extra genital or extragenital or (outside adj3 pelvi?) or (beyond adj3 pelvi?) or gastrointestin$ or intestin$ or urinary or bowel or colorectal or colon$ or diaphragm$).ti,ab,kw.	2008129
46	((endometrio$ adj3 extrapelvic) or (endometrio$ adj3 extra-pelvic) or (endometrio$ adj3 extragenital) or (endometrio$ adj3 extra-genital) or (endometrio$ adj3 gastrointesin$) or (endometrio$ adj3 intesin$) or (endometrio$ adj3 urinary) or (endometrio$ adj3 bowel) or (endometrio$ adj3 colorectal) or (endometrio$ adj3 colon$) or (endometrio$ adj3 diaphragm$) or endometrial implant).ti,ab,kw.	2164
47	38 and (45 or 46)	185
48	limit 47 to yr="2009 - 2015" **[Extra pelvic population 2009-2015]**	79
49	menopause/ or postmenopause/ or (menopaus$ or postmenopaus$ or post-menopaus$).ti,ab,kw.	157041
50	38 and 49	82
51	limit 50 to yr="2009 - 2015" **[Postmenopausal population 2009-2015]**	39
52	pregnancy/ or pregnant woman/ or pregnan$.ti,ab,kw.	1012430
53	38 and 52	196
54	limit 53 to yr="2009 - 2015" **[Pregnant population 2009-2015]**	80

Diagnosis

Endometriosis

Q5a. What is the diagnostic performance of clinical examination, ultrasound, CT scan, MRI, biomarkers, and surgery in diagnosing endometriosis?

Table App 35 Diagnosis of endometriosis – MEDLINE search strings

No.	Query	Results
1	ENDOMETRIOSIS/ or (endometriosis or endometrioma?).ti,ab.	27,050
2	exp Ultrasonography/ or Tomography, X-Ray Computed/ or (ultraso$ or echo$ or sono$ or computed tomography).ti,ab,kw. or (CT adj2 (scan$ or imag$)).ti,ab,kw.	1175435

No.	Query	Results
3	Physical Examination/ or (primary care and (evaluat$ or examin$ or assess$)).ti,ab,kw. or ((physical or clinical) adj3 (examin$ or evaluat$ or assess$)).ti,ab,kw. or ((physician? or clinic?) adj3 (examin$ or evaluat$ or assess$)).ti,ab,kw.	462997
4	((abdom$ or transabdom$ or vagina$ or transvagina$ or rect$ or transrect$) adj2 (US or USS)).ti,ab. or exp MAGNETIC RESONANCE IMAGING/ or (MRI or NMRI).ti,ab. or ((magnetic resonance or MR or MTC or MT or NMR or magneti#ation transfer or spin or chemical shift) adj2 (imag$ or tomogra$)).ti,ab.	573273
5	or/2-4	1965721
6	BIOLOGICAL MARKERS/ or TUMOR MARKERS, BIOLOGICAL/ or CA-125 ANTIGEN/ or EPIDIDYMAL SECRETORY PROTEINS/ or (CA 125 or CA125 or "HE 4" or HE4).ti,ab. or ((human epididymis or human epididymal) adj2 (protein E4 or protein 4 or protein four)).ti,ab. or WAP four disulphide core domain protein.ti,ab.	399729
7	exp BIOPSY/ or biops$.ti,ab. or ((nerve or neural) adj2 (fiber? or fibre?)).ti,ab.	560877
8	exp NERVE FIBERS/pa [Pathology]	20300
9	7 or 8	575537
10	MINIMALLY INVASIVE SURGICAL PROCEDURES/ or LAPAROSCOPES/ or LAPAROTOMY/ or GYNECOLOGIC SURGICAL PROCEDURES/ or *LAPAROSCOPY/ or CYSTOSCOPY/ or exp COLONOSCOPY/ or ((laparoscop$ or laparot$ or cystoscop$ or colonoscop$ or sigmoidoscop$) adj3 diagnos$).ti,ab. or (surg$ adj3 diagnos$).ti. or exp HISTOLOGY/ or exp HISTOLOGICAL TECHNIQUES/ or ((histolog$ or histopath$) adj3 (diagnos$ or confirm$)).ti,ab.	964085
11	exp "SENSITIVITY AND SPECIFICITY"/ or (sensitivity or specificity).ti,ab. or ((pre test or pretest or post test or posttest) adj probability).ti,ab. or (predictive value$ or PPV or NPV).ti,ab. or likelihood ratio$.ti,ab. or LIKELIHOOD FUNCTIONS/ or (ROC curve$ or AUC).ti,ab. or diagnos$.ti. or (diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab. or gold standard.ab. or "Quality of Life"/ or (quality of life or QoL).ti,ab,kw.	2314442
12	1 and (5 or 6 or 9 or 10)	9651
13	11 and 12	2151
14	(5 or 6 or 9 or 10) and *ENDOMETRIOSIS/di [Diagnosis]	1232
15	(5 or 6 or 9 or 10) and *ENDOMETRIOSIS/pa [Pathology]	935
16	Endometriosis/dg [Diagnostic Imaging]	1158
17	or/13-16	4237
18	limit 17 to english language	3543
19	18 not ((LETTER/ or EDITORIAL/ or NEWS/ or exp HISTORICAL ARTICLE/ or ANECDOTES AS TOPIC/ or COMMENT/ or CASE REPORT/ or (letter or comment*).ti.) not (RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.))	2535
20	19 not ((ANIMALS/ not HUMANS/) or exp ANIMALS, LABORATORY/ or exp ANIMAL EXPERIMENTATION/ or exp MODELS, ANIMAL/ or exp RODENTIA/ or (rat or rats or mouse or mice).ti.)	2447
21	limit 20 to yr="2016-2019" **[All populations 2016-2019]**	492
22	exp meta-analysis/ or meta-analysis.mp. or metaanalysis.mp. or systematic review.mp. or systematic literature review.mp. or pooled analysis.mp. or (exp review literature as topic/ and systematic.mp.)	266009
23	Clinical trial/ or Randomized controlled trial/ or Random allocation/ or Double-blind method/ or Cross-over studies/ or (Randomi#ed controlled trial$ or randomi#ed trial$ or rct or random allocation or randomly allocated or allocated randomly or (allocat$ adj3 random) or single blind$ or double blind$ or (((treble or triple) adj blind$) or placebo$)).tw.	1113085
24	21 and 22 **[SRs]**	27
25	(21 and 23) not 24 **[RCTs]**	11
26	21 not (24 or 25) **[Other studies]**	454
27	limit 20 to yr="2009-2015"	819
28	(extrapelvic or extra pelvic or extra genital or extragenital or (outside adj3 pelvi?) or (beyond adj3 pelvi?) or gastrointestin$ or intestin$ or urinary or bowel or colorectal or colon$ or diaphragm$ or endometrial implant).ti,ab,kw.	1412131
29	27 and 28 **[Extra pelvic population 2009-2015]**	184
30	menopause/ or postmenopause/ or (menopaus$ or postmenopaus$ or post-menopaus$).ti,ab,kw.	97860
31	(27 and 30) not 29 **[Postmenopausal population 2009-2015]**	27
32	Pregnancy/ or Pregnant Women/ or pregnan$.ti,ab,kw.	968482
33	(27 and 32) not (29 or 31) **[Pregnant population 2009-2015]**	67
34	Tomography, X-Ray Computed/ or (CT or computed tomography).ti,ab,kw.	628744
35	Physical Examination/ or (primary care and (evaluat$ or examin$ or assess$)).ti,ab,kw. or ((physical or clinical) adj3 (examin$ or evaluat$ or assess$)).ti,ab,kw. or ((physician? or clinic?) adj3 (examin$ or evaluat$ or assess$)).ti,ab,kw.	462997
36	(27 and (34 or 35)) not (29 or 31 or 33) **[Extra interventions 2009-2015]**	59

Table App 36 Diagnosis of endometriosis – EMBASE search strings

No.	Query	Results
1	ENDOMETRIOSIS/ or (endometriosis or endometrioma?).ti,ab.	42,776
2	physical examination/ or clinical assessment/ or clinical evaluation/ or clinical examination/ or (primary care and (evaluat$ or examin$ or assess$)).ti,ab,kw. or ((physical or clinical) adj3 (examin$ or evaluat$ or assess$)).ti,ab,kw. or ((physician? or clinic?) adj3 (examin$ or evaluat$ or assess$)).ti,ab,kw.	1,068,012
3	exp ECHOGRAPHY/ or x-ray computed tomography/ or computer assisted tomography/ or (ultraso$ or echo$ or sono$ or CT or computed tomography).ti,ab,kw.	2,075,286
4	((abdom$ or transabdom$ or vagina$ or transvagina$ or rect$ or transrect$) adj2 (US or USS)).ti,ab. or exp NUCLEAR MAGNETIC RESONANCE IMAGING/ or (MRI or NMRI).ti,ab. or ((magnetic resonance or MR or MTC or MT or NMR or magneti#ation transfer or spin or chemical shift) adj2 (imag$ or tomogra$)).ti,ab.	981,237
5	TUMOR MARKER/ or CA 125 ANTIGEN/ or HUMAN EPIDIDYMIS PROTEIN 4/ or EPIDIDYMAL SECRETORY PROTEIN/ or (CA 125 or CA125 or "HE 4" or HE4).ti,ab. or ((human epididymis or human epididymal) adj2 (protein E4 or protein 4 or protein four)).ti,ab. or WAP four disulphide core domain protein.ti,ab.	92,568
6	((ENDOMETRIUM BIOPSY/ or *BIOPSY/) and *NERVE FIBER/) or biops$.ti,ab. or ((nerve or neural) adj2 (fiber? or fibre?)).ti,ab.	679,185
7	*MINIMALLY INVASIVE SURGERY/ or *LAPAROSCOPE/ or *LAPAROTOMY/ or *GYNECOLOGIC SURGERY/ or *LAPAROSCOPY/ or *CYSTOSCOPY/ or *COLONOSCOPY/ or *SIGMOIDOSCOPY/ or ((laparoscop$ or laparot$ or cystoscop$ or colonoscop$ or sigmoidoscop$) adj3 diagnos$).ti,ab. or (surg$ adj3 diagnos$).ti. or exp *HISTOLOGY/ or ((histolog$ or histopath$) adj3 (diagnos$ or confirm$)).ti,ab.	273,625
8	"SENSITIVITY AND SPECIFICITY"/ or (sensitivity or specificity).ti,ab. or ((pre test or pretest or post test or posttest) adj probability).ti,ab. or (predictive value$ or PPV or NPV).ti,ab. or likelihood ratio$.ti,ab. or STATISTICAL MODEL/ or (ROC curve$ or AUC).ti,ab. or diagnos$.ti. or (diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab. or gold standard.ab. or *DIAGNOSTIC ACCURACY/ or DIAGNOSTIC TEST ACCURACY STUDY/ or exp "quality of life"/ or (quality of life or QoL).ti,ab,kw.	3,049,324
9	or/2-7	4,223,706
10	1 and 8 and 9	3,318
11	9 and *ENDOMETRIOSIS/di [Diagnosis]	2,836
12	*ENDOMETRIOSIS/ and (*DIAGNOSTIC IMAGING/ or *GYNECOLOGICAL EXAMINATION/)	254
13	or/10-12	5,369
14	limit 13 to english language	4,679
15	14 not ((letter.pt. or LETTER/ or note.pt. or editorial.pt. or CASE REPORT/ or CASE STUDY/ or (letter or comment*).ti.) not (RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.))	3,332
16	15 not ((ANIMAL/ not HUMAN/) or NONHUMAN/ or exp ANIMAL EXPERIMENT/ or exp EXPERIMENTAL ANIMAL/ or ANIMAL MODEL/ or exp RODENT/ or (rat or rats or mouse or mice).ti.)	3,163
17	limit 16 to yr="2016-2019" **[All populations 2016-2019]**	786
18	meta-analysis/ or meta-analysis.mp. or metaanalysis.mp. or systematic review/ or systematic review.mp. or systematic literature review.mp. or pooled analysis.mp.	433,522
19	clinical trial/ or randomized controlled trial/ or randomization/ or crossover procedure/ or (randomi#ed controlled trial$ or randomi#ed trial$ or rct or (allocat$ adj3 random$) or single blind$ or double blind$ or placebo$).tw.	1,671,254
20	17 and 18 **[SRs]**	57
21	(17 and 19) not 20 **[RCTs]**	53
22	17 not (20 or 21) **[Other studies]**	676
23	limit 16 to yr="2009-2015"	1,447
24	(extrapelvic or extra pelvic or extra genital or extragenital or (outside adj3 pelvi?) or (beyond adj3 pelvi?) or gastrointestin$ or intestin$ or urinary or bowel or colorectal or colon$ or diaphragm$ or endometrial implant$).ti,ab,kw.	2,009,208
25	23 and 24 **[Extra pelvic population 2009-2015]**	393
26	18 and 25 **[SRs]**	20
27	(25 and 19) not 26 **[RCTs]**	20
28	25 not (26 or 27) **[Other studies]**	353
29	menopause/ or postmenopause/ or (menopaus$ or postmenopaus$ or post-menopaus$).ti,ab,kw.	157,070
30	(23 and 29) not 25 **[Postmenopausal population 2009-2015]**	71
31	pregnancy/ or pregnant woman/ or pregnan$.ti,ab,kw.	1,012,975
32	(23 and 31) not (25 or 30) **[Pregnant population 2009-2015]**	125
33	computer assisted tomography/ or x-ray computed tomography/ or (CT or computed tomography).ti,ab,kw.	1,096,312

No.	Query	Results
34	Physical Examination/ or (primary care and (evaluat$ or examin$ or assess$)).ti,ab,kw. or ((physical or clinical) adj3 (examin$ or evaluat$ or assess$)).ti,ab,kw. or ((physician? or clinic?) adj3 (examin$ or evaluat$ or assess$)).ti,ab,kw.	817,570
35	33 or 34	1,822,534
36	(23 and 35) not (25 or 30 or 32) **[Extra interventions 2009-2015]**	147

Adenomyosis

Q5b. What is the diagnostic performance of ultrasound and MRI in diagnosing adenomyosis?

Table App 37 Diagnosis of adenomyosis – MEDLINE search strings

No.	Query	Results
1	ADENOMYOSIS/ or (adenomyosis or adenomyoma? or adenometritis or adenomyositis or adenomyometritis).ti,ab,kw.	3,065
2	exp ULTRASONOGRAPHY/ or (ultraso$ or echo$ or sono$).ti,ab. or ((abdom$ or transabdom$ or vagina$ or transvagina$ or rect$ or transrect$) adj2 (US or USS)).ti,ab. or exp MAGNETIC RESONANCE IMAGING/ or (MRI or NMRI).ti,ab. or ((magnetic resonance or MR or MTC or MT or NMR or magneti#ation transfer or spin or chemical shift) adj2 (imag$ or tomogra$)).ti,ab.	1,198,174
3	exp "SENSITIVITY AND SPECIFICITY"/ or (sensitivity or specificity).ti,ab. or ((pre test or pretest or post test or posttest) adj probability).ti,ab. or (predictive value$ or PPV or NPV).ti,ab. or likelihood ratio$.ti,ab. or LIKELIHOOD FUNCTIONS/ or (ROC curve$ or AUC).ti,ab. or diagnos$.ti. or (diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab. or gold standard.ab.	2,022,679
4	1 and 2 AND 3	259
5	(2 or 3) and (*ADENOMYOSIS/di or *ADENOMYOSIS/dg)	74
6	*ADENOMYOSIS/ and (*DIAGNOSTIC IMAGING/ or *"DIAGNOSTIC TECHNIQUES, OBSTETRICAL AND GYNECOLOGICAL"/)	1
7	or/4-6	305
8	limit 7 to english language	259
9	8 not (((LETTER/ or EDITORIAL/ or NEWS/ or exp HISTORICAL ARTICLE/ or ANECDOTES AS TOPIC/ or COMMENT/ or CASE REPORT/ or (letter or comment*).ti.) not RANDOMIZED CONTROLLED TRIAL/) or random*.ti,ab.)	211
10	9 not ((ANIMALS/ not HUMANS/) or exp ANIMALS, LABORATORY/ or exp ANIMAL EXPERIMENTATION/ or exp MODELS, ANIMAL/ or exp RODENTIA/ or (rat or rats or mouse or mice).ti.)	211
11	limit 10 to yr="2009-2019" **[Adenomyosis population 2009-2019]**	142

Table App 38 Diagnosis of adenomyosis – EMBASE search strings

No.	Query	Results
1	ADENOMYOSIS/ or (adenomyosis or adenomyoma? or adenometritis or adenomyositis or adenomyometritis).ti,ab,kw.	6,414
2	exp ECHOGRAPHY/ or (ultraso$ or echo$ or sono$).ti,ab,kw.	1,161,389
3	((abdom$ or transabdom$ or vagina$ or transvagina$ or rect$ or transrect$) adj2 (US or USS)).ti,ab. or exp NUCLEAR MAGNETIC RESONANCE IMAGING/ or (MRI or NMRI).ti,ab. or ((magnetic resonance or MR or MTC or MT or NMR or magneti#ation transfer or spin or chemical shift) adj2 (imag$ or tomogra$)).ti,ab.	982,122
4	"SENSITIVITY AND SPECIFICITY"/ or (sensitivity or specificity).ti,ab. or ((pre test or pretest or post test or posttest) adj probability).ti,ab. or (predictive value$ or PPV or NPV).ti,ab. or likelihood ratio$.ti,ab. or STATISTICAL MODEL/ or (ROC curve$ or AUC).ti,ab. or diagnos$.ti. or (diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab. or gold standard.ab. or *DIAGNOSTIC ACCURACY/ or DIAGNOSTIC TEST ACCURACY STUDY/ or exp "quality of life"/ or (quality of life or QoL).ti,ab,kw.	3,051,535
5	or/2-3	1,969,421
6	1 and 4 and 5	645
7	5 and *ADENOMYOSIS/di	354
8	*ADENOMYOSIS/ and *DIAGNOSTIC IMAGING/	7
9	or/6-8	865
10	limit 9 to english language	773
11	10 not ((letter.pt. or LETTER/ or note.pt. or editorial.pt. or CASE REPORT/ or CASE STUDY/ or (letter or comment*).ti.) not (RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.))	600

No.	Query	Results
12	11 not ((ANIMAL/ not HUMAN/) or NONHUMAN/ or exp ANIMAL EXPERIMENT/ or exp EXPERIMENTAL ANIMAL/ or ANIMAL MODEL/ or exp RODENT/ or (rat or rats or mouse or mice).ti.)	581
13	limit 12 to yr="2009-2019" **[Adenomyosis population 2009-2019]**	439
14	meta-analysis/ or meta-analysis.mp. or metaanalysis.mp. or systematic review/ or systematic review.mp. or systematic literature review.mp. or pooled analysis.mp.	434,175
15	clinical trial/ or randomized controlled trial/ or randomization/ or crossover procedure/ or (randomi#ed controlled trial$ or randomi#ed trial$ or rct or (allocat$ adj3 random$) or single blind$ or double blind$ or placebo$).tw.	1,672,252
16	13 and 14 **[SRs]**	23
17	(13 and 15) not 16 **[RCTs]**	28
18	13 not (16 or 17) **[Other studies]**	388

Systems that can guide treatment

Q6. Do staging systems to guide treatment in people with endometriosis improve patient outcomes?

Table App 39 Systems that can guide treatment – MEDLINE search strings

No.	Query	Results
1	ENDOMETRIOSIS/	21,088
2	ADENOMYOSIS/	653
3	(endometrios#s or endometrioma? or adenomyos#s or adenomyoma? or adenometrit#s or adenomyosit#s or adenomyometrit#s).ti,ab.	25,101
4	or/1-3	28,485
5	INTERNATIONAL CLASSIFICATION OF DISEASES/	7,690
6	CLASSIFICATION/	10,014
7	TERMINOLOGY AS TOPIC/	54,412
8	(Endometriosis Fertility Index or EFI or Enzian).ti,ab.	286
9	((surg$ or laparoscop$) adj3 (classif$ or scor$ or stage? or staging or categor$ or visuali$)).ti,ab.	36,097
10	or/5-9	107,354
11	and/4,10	475
12	SEVERITY OF ILLNESS INDEX/	232,125
13	DISEASE PROGRESSION.mp. or Disease Progression/	205,592
14	NEOPLASM STAGING/	167,114
15	or/12-14	580,394
16	and/4,15	1,168
17	*ENDOMETRIOSIS/pa [Pathology]	2,271
18	or/16-17	3,297
19	((American Fertility Society or AFS or rAFS or American Society for Reproductive Medicine or ASRM or rASRM) adj2 (classif$ or scor$ or stage? or staging or categor$)).ti,ab.	674
20	(disease adj2 (grad$ or classif$ or index$ or indices or stage? or staging or score? or scoring or categor$)).ti,ab.	124,834
21	((endometrios#s or endometrioma?) adj5 (grad$ or classif$ or index$ or indices or stage? or staging or score? or scoring or categor$)).ti,ab.	1,793
22	or/19-21	126,783
23	and/18,22	492
24	*ENDOMETRIOSIS/cl [Classification]	89
25	or/11,23-24	956
26	limit 25 to english language	846
27	LETTER/	1,046,012
28	EDITORIAL/	504,717
29	NEWS/	197,536
30	exp HISTORICAL ARTICLE/	391,354

No.	Query	Results
31	ANECDOTES AS TOPIC/	4,732
32	COMMENT/	807,916
33	CASE REPORT/	2,049,714
34	(letter or comment*).ti.	143,661
35	or/27-34	4,224,419
36	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.	1,200,635
37	35 not 36	4,199,553
38	ANIMALS/ not HUMANS/	4,594,539
39	exp ANIMALS, LABORATORY/	851,769
40	exp ANIMAL EXPERIMENTATION/	9,176
41	exp MODELS, ANIMAL/	547,052
42	exp RODENTIA/	3,153,032
43	(rat or rats or mouse or mice).ti.	1,305,359
44	or/37-43	9,543,783
45	26 not 44	759
46	limit 45 to yr="2016-2019" **[All populations 2016-2019]**	148
47	limit 45 to yr="2009-2015"	240
48	(extrapelvic or extra pelvic or extra genital or extragenital or (outside adj3 pelvi?) or (beyond adj3 pelvi?) or gastrointestin$ or intestin$ or urinary or bowel or colorectal or colon$ or diaphragm$ or endometrial implant).ti,ab,kw.	1,412,131
49	47 AND 48 **[All populations 2016-2019]**	34
50	menopause/ or postmenopause/ or (menopaus$ or postmenopaus$ or post-menopaus$).ti,ab,kw.	97,860
51	47 AND 50 **[Postmenopausal population 2009-2015]**	2
52	Pregnancy/ or Pregnant Women/ or pregnan$.ti,ab,kw.	968,482
53	47 AND 52 **[Pregnant population 2009-2015]**	39

Table App 40 Staging systems – EMBASE search strings

No.	Query	Results
1	*ENDOMETRIOSIS/	25,042
2	*ADENOMYOSIS/	2,234
3	(endometrios#s or endometrioma? or adenomyos#s or adenomyoma? or adenometrit#s or adenomyosit#s or adenomyometrit#s).ti,ab.	38,727
4	or/1-3	40,572
5	SEVERITY OF ILLNESS INDEX/	14,885
6	NOMENCLATURE/	60,048
7	(Endometriosis Fertility Index or EFI or Enzian).ti,ab.	551
8	or/5-7	75,450
9	and/4,8	174
10	exp *DISEASE CLASSIFICATION/	56,050
11	DISEASE SEVERITY/	543,933
12	DISEASE COURSE/	458,025
13	exp CLASSIFICATION/	2,101,365
14	or/10-13	2,961,319
15	and/4,14	4,737
16	((American Fertility Society or AFS or rAFS or American Society for Reproductive Medicine or ASRM or rASRM) adj2 (classif$ or scor$ or stage? or staging or categor$)).ti,ab.	1,131
17	((surg$ or laparoscop$) adj3 (classif$ or scor$ or stage? or staging or categor$ or visuali$)).ti,ab.	56,069
18	(disease adj2 (grad$ or classif$ or index$ or indices or stage? or staging or score? or scoring or categor$)).ti,ab.	200,801
19	((endometrios#s or endometrioma?) adj5 (grad$ or classif$ or index$ or indices or stage? or staging or score? or scoring or categor$)).ti,ab.	3,054

No.	Query	Results
20	or/16-19	256,316
21	and/15,20	1,394
22	or/9,21	1,515
23	limit 22 to english language	1,398
24	letter.pt. or LETTER/	1,095,318
25	note.pt.	775,951
26	editorial.pt.	634,717
27	CASE REPORT/ or CASE STUDY/	2,578,494
28	(letter or comment*).ti.	199,107
29	or/24-28	4,873,409
30	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.	1,584,604
31	29 not 30	4,829,533
32	ANIMAL/ not HUMAN/	1,464,294
33	NONHUMAN/	5,984,520
34	exp ANIMAL EXPERIMENT/	2,468,336
35	exp EXPERIMENTAL ANIMAL/	676,936
36	ANIMAL MODEL/	1,276,806
37	exp RODENT/	3,921,449
38	(rat or rats or mouse or mice).ti.	1,640,666
39	or/31-38	13,234,017
40	23 not 39	1,292
41	limit 40 to yr="2016-2019" **[All populations 2016-2019]**	324
42	limit 40 to yr="2009-2015"	592
43	meta-analysis/ or meta-analysis.mp. or metaanalysis.mp. or systematic review/ or systematic review.mp. or systematic literature review.mp. or pooled analysis.mp.	433,322
44	clinical trial/ or randomized controlled trial/ or randomization/ or crossover procedure/ or (randomi#ed controlled trial$ or randomi#ed trial$ or rct or (allocat$ adj3 random$) or single blind$ or double blind$ or placebo$).tw.	1,671,042
45	41 AND 43 **[SRs]**	14
46	41 AND 44 NOT 45 **[RCTs]**	22
47	41 NOT (45 OR 46) **[Other studies]**	288
48	(extrapelvic or extra pelvic or extra genital or extragenital or (outside adj3 pelvi?) or (beyond adj3 pelvi?) or gastrointestin$ or intestin$ or urinary or bowel or colorectal or colon$ or diaphragm$ or endometrial implant$).ti,ab,kw.	2,008,961
49	42 AND 48 **[Extra pelvic population 2009-2015]**	86
50	menopause/ or postmenopause/ or (menopaus$ or postmenopaus$ or post-menopaus$).ti,ab,kw.	157,056
51	42 AND 50 NOT 49 **[Postmenopausal population 2009-2015]**	15
52	pregnancy/ or pregnant woman/ or pregnan$.ti,ab,kw.	1,012,616
53	42 AND 52 NOT (49 OR 51) **[Pregnant population 2009-2015]**	111

Treatment

Pharmacological management – Analgesics

Q7a. In people with endometriosis or adenomyosis, are analgesics effective for managing endometriosis- or adenomyosis-associated pain?

Table App 41 Analgesics – MEDLINE search strings

No.	Query	Results
1	ENDOMETRIOSIS/	21,083
2	ADENOMYOSIS/	652

No.	Query	Results
3	(endometriosis or endometrioma? or adenomyos#s or adenomyoma? or adenometrit#s or adenomyosit#s or adenomyometrit#s).ti,ab.	25,070
4	or/1-3	28,465
5	exp ANALGESIA/	42,836
6	exp ANALGESICS/	526,627
7	(analgesi$ or painkiller? or pain killer? or cannabis).ti,ab.or cannabis/	138,919
8	(pain adj2 relie$).ti,ab.	42,348
9	exp ANALGESICS, NON-NARCOTIC/	328,014
10	exp ANTI-INFLAMMATORY AGENTS, NON-STEROIDAL/	200,314
11	CYCLOOXYGENASE 2 INHIBITORS/	8,901
12	exp NARCOTICS/ cannabis/ or (cannabis).ti,ab.	120,056
13	(NSAID? or coxib? or narcotic? or nonnarcotic? or opioid? or nonopioid? or opiate? or nonopiate?).ti,ab.	136,767
14	((nonsteroid$ or non steroid$) adj2 (antiinflammat$ or anti inflammat$)).ti,ab.	37,747
15	((COX2 or COX 2 or cyclo?xygenase$) adj2 inhibit$).ti,ab.	21,635
16	ACETAMINOPHEN/	17,597
17	DICLOFENAC/	7,616
18	IBUPROFEN/	8,551
19	NAPROXEN/	4,012
20	MEFENAMIC ACID/	1,043
21	exp INDOMETHACIN/	29,965
22	ASPIRIN/	43,921
23	exp CODEINE/	6,791
24	TRAMADOL/	3,008
25	BUPRENORPHINE/	4,899
26	MORPHINE/	37,627
27	(acetaminophen or paracetamol or diclo??enac or ibupro??en or naproxen or celecoxib or me??enamic acid or etoricoxib or indomet?acin or tol??enamic acid or aspirin or acetylsalicylic acid or cocodamol or co codamol or cocodaprin or co codaprin or codydramol or co dydramol or codeine or dihydrocodeine or tramadol or buprenorphine or morphine).mp.	226,258
28	or/5-27	748,619
29	and/4,28	854
30	limit 29 to english language	754
31	LETTER/	1,045,453
32	EDITORIAL/	504,346
33	NEWS/	197,499
34	exp HISTORICAL ARTICLE/	391,324
35	ANECDOTES AS TOPIC/	4,732
36	COMMENT/	807,080
37	CASE REPORT/	2,049,348
38	(letter or comment*).ti.	143,566
39	or/31-38	4,222,894
40	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.	1,199,740
41	39 not 40	4,198,049
42	ANIMALS/ not HUMANS/	4,593,772
43	exp ANIMALS, LABORATORY/	851,606
44	exp ANIMAL EXPERIMENTATION/	9,172
45	exp MODELS, ANIMAL/	546,906
46	exp RODENTIA/	3,152,515
47	(rat or rats or mouse or mice).ti.	1,305,004
48	or/41-47	9,541,152

No.	Query	Results
49	30 not 48	587
50	limit 49 to yr="2016-2019" [All populations 2016-2019]	142
51	(extrapelvic or extra pelvic or extra genital or extragenital or (outside adj3 pelvi?) or (beyond adj3 pelvi?) or gastrointestin$ or intestin$ or urinary or bowel or colorectal or colon$ or diaphragm$).ti,ab,kw.	1,411,330
52	((endometrio$ adj3 extrapelvic) or (endometrio$ adj3 extra-pelvic) or (endometrio$ adj3 extragenital) or (endometrio$ adj3 extra-genital) or (endometrio$ adj3 gastrointesin$) or (endometrio$ adj3 intesin$) or (endometrio$ adj3 urinary) or (endometrio$ adj3 bowel) or (endometrio$ adj3 colorectal) or (endometrio$ adj3 colon$) or (endometrio$ adj3 diaphragm$) or endometrial implant).ti,ab,kw.	1,261
53	49 AND (51 OR 52)	81
54	limit 53 to yr="2009-2015" [Extra pelvic population 2009-2015]	28
55	Pregnancy/ or Pregnant Women/ or pregnan$.ti,ab,kw.	968,169
56	49 AND 55	95
57	limit 56 to yr="2009-2015" [Pregnant population 2009-2015]	27
58	menopause/ or postmenopause/ or (menopaus$ or postmenopaus$ or post-menopaus$).ti,ab,kw.	97,817
59	49 AND 58	19
60	limit 59 to yr="2009-2015" [Postmenopausal population 2009-2015]	5
61	(adenomyosis or adenomyoma? or adenometritis or adenomyositis or adenomyometritis).ti,ab,kw. or ADENOMYOSIS/	3,061
62	(49 AND 61) NOT (54 OR 57 OR 60)	45
63	limit 62 to yr="2009-2015" [Adenomyosis population 2009-2015]	16
64	cannabis/ or (cannabis).ti,ab.	20,281
65	4 AND 64 NOT 48	2
66	limit 65 to yr="2009-2015"	-0
67	limit 66 to english language [Cannabis 2009-2015]	0

Table App 42 Analgesics – EMBASE search strings

No.	Query	Results
1	ENDOMETRIOSIS/ or ADENOMYOSIS/ or (endometriosis or endometrioma? or adenomyos#s or adenomyoma? or adenometrit#s or adenomyosit#s or adenomyometrit#s).ti,ab.	46,676
2	exp *ANALGESIA/ or exp *ANALGESIC AGENT/ or (analgesi$ or painkiller? or pain killer? or cannabis).ti,ab. or cannabis/ or medical cannabis/ or (pain adj2 relie$).ti,ab. or exp *NONSTEROID ANTIINFLAMMATORY AGENT/ or exp *CYCLOOXYGENASE 2 INHIBITOR/ or exp *NARCOTIC ANALGESIC AGENT/ or (NSAID? or coxib? or narcotic? or nonnarcotic? or opioid? or nonopioid? or opiate? or nonopiate?).ti,ab. or ((nonsteroid$ or non steroid$) adj2 (antiinflammat$ or anti inflammat$)).ti,ab. or ((COX2 or COX 2 or cyclo?xygenase$) adj2 inhibit$).ti,ab. or *PARACETAMOL/ or *DICLOFENAC/ or DICLOFENAC POTASSIUM/ or DICLOFENAC DERIVATIVE/ or *IBUPROFEN/ or IBUPROFEN DERIVATIVE/ or *NAPROXEN/ or *CELECOXIB/ or *MEFENAMIC ACID/ or *ETORICOXIB/ or *INDOMETACIN/ or *TOLFENAMIC ACID/ or *ACETYLSALICYLIC ACID/ or *COCODAMOL/ or *ACETYLSALICYLIC ACID PLUS CODEINE PHOSPHATE/ or *CODYDRAMOL/ or *CODEINE/ or CODEINE PHOSPHATE/ or *DIHYDROCODEINE/ or *TRAMADOL/ or *BUPRENORPHINE/ or *MORPHINE/ or MORPHINE SULPHATE/ or (acetaminophen or paracetamol or diclo??enac or ibupro??en or naproxen or celecoxib or me??enamic acid or etoricoxib or indomet?acin or tol??enamic acid or aspirin or acetylsalicylic acid or cocodamol or co codamol or cocodaprin or co codaprin or codydramol or co dydramol or codeine or dihydrocodeine or tramadol or buprenorphine or morphine).mp.	1,068,226
3	1 and 2	1,869
4	limit 3 to english language	1,711
5	4 not ((letter.pt. or LETTER/ or note.pt. or editorial.pt. or CASE REPORT/ or CASE STUDY/ or (letter or comment*).ti.) not (RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.))	1,458
6	5 not ((ANIMAL/ not HUMAN/) or NONHUMAN/ or exp ANIMAL EXPERIMENT/ or exp EXPERIMENTAL ANIMAL/ or ANIMAL MODEL/ or exp RODENT/ or (rat or rats or mouse or mice).ti.)	1,247
7	limit 6 to yr="2016-2019" [All populations 2016-2019]	305
8	meta-analysis/ or meta-analysis.mp. or metaanalysis.mp. or systematic review/ or systematic review.mp. or systematic literature review.mp. or pooled analysis.mp.	433,848
9	clinical trial/ or randomized controlled trial/ or randomization/ or crossover procedure/ or (randomi#ed controlled trial$ or randomi#ed trial$ or rct or (allocat$ adj3 random$) or single blind$ or double blind$ or placebo$).tw.	1,671,620
10	7 and 8 [SRs]	38
11	(7 and 9) not 10 [RCTs]	56

No.	Query	Results
12	7 not (10 or 11) **[Other studies]**	211
13	limit 6 to yr="2009-2015"	532
14	(extrapelvic or extra pelvic or extra genital or extragenital or (outside adj3 pelvi?) or (beyond adj3 pelvi?) or gastrointestin$ or intestin$ or urinary or bowel or colorectal or colon$ or diaphragm$ or endometrial implant$).ti,ab,kw.	2,009,712
15	13 and 14 **[Extra pelvic population 2009-2015]**	116
16	menopause/ or postmenopause/ or (menopaus$ or postmenopaus$ or post-menopaus$).ti,ab,kw.	157,097
17	(13 and 16) not 15 **[Postmenopausal population 2009-2015]**	23
18	pregnancy/ or pregnant woman/ or pregnan$.ti,ab,kw.	1,013,166
19	(13 and 18) not (15 or 17) **[Pregnant population 2009-2015]**	78
20	(adenomyosis or adenomyoma? or adenometritis or adenomyositis or adenomyometritis).ti,ab,kw. or ADENOMYOSIS/	6,389
21	(13 and 20) not (15 or 17 or 19) **[Adenomyosis population 2009-2015]**	67
22	cannabis.ti,ab. or cannabis/ or medical cannabis/	43,854
23	(13 and 22) not (15 or 17 or 19 or 21) **[Cannabis 2009-2015]**	1

Pharmacological management – Neuromodulators

Q7b. In people with endometriosis or adenomyosis, are neuromodulators effective for managing endometriosis- or adenomyosis- associated pain?

Table App 43 Neuromodulators – MEDLINE search strings

No.	Query	Results
1	ENDOMETRIOSIS/	21,088
2	ADENOMYOSIS/	653
3	(endometriosis or endometrioma? or adenomyos#s or adenomyoma? or adenometrit#s or adenomyosit#s or adenomyometrit#s).ti,ab.	25,085
4	or/1-3	28,480
5	(Neuro-modulat$ or neuromodulat$).ti,ab.	15,308
6	exp NEURALGIA/ and exp ANALGESICS/	3,755
7	((neuropathic pain or neuralg$) adj3 (analgesi$ or drug$ or agent? or med$)).ti,ab.	1,594
8	exp ANTIDEPRESSIVE AGENTS, TRICYCLIC/	30,895
9	(tricyclic$ adj2 (antidepress$ or anti-depress$ or drug$ or agent$ or med$)).ti,ab.	10,272
10	(Amitriptyline or Clomipramine or Desipramine or Dothiepin or Doxepin or Imipramine or Iprindole or Lofepramine or Nortriptyline or Opipramol or Protriptyline or Trimipramine).mp.	32,310
11	(Serotonin norepinephrine reuptake inhibitor? or Serotonin norepinephrine re uptake inhibitor?).ti,ab.	1,038
12	(serotonin noradrenaline reuptake inhibitor? or serotonin noradrenaline re uptake inhibitor?).ti,ab.	304
13	SNRI.ti,ab.	783
14	(duloxetine or mirtazapine or venlafaxine or Desvenlafaxine or Milnacipran or Levomilnacipran or Sibutramine).mp.	10,086
15	exp ANESTHETICS, LOCAL/	102,897
16	((local or conduction or block$ or topical) adj3 an?esthe$).ti,ab.	50,353
17	(Benzocaine or Benzyl Alcohol or Bupivacaine or Carticaine or Cocaine or Dibucaine or Diphenhydramine or Ethyl Chloride or Etidocaine or Lidocaine or Mepivacaine or Prilocaine or Procaine or Propoxycaine or Tetracaine or Tetrodotoxin or Trimecaine).mp.	133,024
18	CAPSAICIN/	10,204
19	Capsaicin?.mp.	14,724
20	((N-METHYL-D-ASPARTATE or NMDA) adj3 (block$ or antagon$)).ti,ab.	18,440
21	KETAMINE/	11,947
22	Ketamin?.mp.	19,168
23	exp ANTICONVULSANTS/	139,236
24	(Anti convuls$ or anticonvuls$ or anti epilep$ or antiepilep$).ti,ab.	48,194

No.	Query	Results
25	(Acetazolamide or Bromide? or Carbamazepine or Chlormethiazole or Clonazepam or Clorazepate Dipotassium or Diazepam or Dimethadione or Estazolam or Ethosuximide or Flunarizine or Lorazepam or Magnesium Sulfate or Medazepam or Mephenytoin or Mephobarbital or Meprobamate or Nitrazepam or Paraldehyde or Phenobarbital or Phenytoin or Primidone or Riluzole or Thiopental or Tiletamine or Trimethadione or Valproic Acid or Valproate or Topiramate or Vigabatrin or Gabapentin or Neurontin or Pregabalin or Lyrica or Tiagabine or Gabitril).mp.	202,962
26	exp NERVE BLOCK/	21,382
27	(nerve? adj3 block$).ti,ab.	13,433
28	(chemical adj3 neurolys?s).ti,ab.	75
29	chemodenervation?.ti,ab.	355
30	exp NERVOUS SYSTEM/ and exp ABLATION TECHNIQUES/	4,292
31	(nerve? adj3 ablat$).ti,ab.	657
32	exp DENERVATION/	72,188
33	Denervation?.ti,ab.	21,383
34	or/5-33	589,388
35	4 and 34	268
36	limit 35 to english language	242
37	LETTER/	1,046,012
38	EDITORIAL/	504,717
39	NEWS/	197,536
40	exp HISTORICAL ARTICLE/	391,354
41	ANECDOTES AS TOPIC/	4,732
42	COMMENT/	807,916
43	CASE REPORT/	2,049,714
44	(letter or comment*).ti.	143,661
45	or/37-44	4,224,419
46	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.	1,200,635
47	45 not 46	4,199,553
48	ANIMALS/ not HUMANS/	4,594,539
49	exp ANIMALS, LABORATORY/	851,769
50	exp ANIMAL EXPERIMENTATION/	9,176
51	exp MODELS, ANIMAL/	547,052
52	exp RODENTIA/	3,153,032
53	(rat or rats or mouse or mice).ti.	1,305,359
54	or/47-53	9,543,783
55	36 not 54	196
56	limit 55 to yr="2016-2019" **[All populations 2016-2019]**	27
57	limit 55 to yr="2009-2015"	55
58	(extrapelvic or extra pelvic or extra genital or extragenital or (outside adj3 pelvi?) or (beyond adj3 pelvi?) or gastrointestin$ or intestin$ or urinary or bowel or colorectal or colon$ or diaphragm$ or endometrial implant).ti,ab,kw.	1,412,131
59	57 AND 58 **[Extra pelvic population 2009-2015]**	10
60	menopause/ or postmenopause/ or (menopaus$ or postmenopaus$ or post-menopaus$).ti,ab,kw.	97,860
61	57 AND 60 **[Postmenopausal population 2009-2015]**	-
62	Pregnancy/ or Pregnant Women/ or pregnan$.ti,ab,kw.	968,482
63	57 AND 62 **[Pregnant population 2009-2015]**	2
64	(adenomyosis or adenomyoma? or adenometritis or adenomyositis or adenomyometritis).ti,ab,kw. or ADENOMYOSIS/	3,063
65	57 AND 64 NOT (59 OR 61 OR 63) **[Adenomyosis population 2009-2015]**	4

Table App 44 Neuromodulators – EMBASE search strings

No.	Query	Results
1	*ENDOMETRIOSIS/	25,042
2	*ADENOMYOSIS/	2,234
3	(endometriosis or endometrioma? or adenomyos#s or adenomyoma? or adenometrit#s or adenomyosit#s or adenomyometrit#s).ti,ab.	38,697
4	or/1-3	40,549
5	(Neuro-modulat$ or neuromodulat$).ti,ab.	21,756
6	exp *NEURALGIA/ and exp *ANALGESIC AGENT/	3,740
7	((neuropathic pain or neuralg$) adj3 (analgesi$ or drug$ or agent? or med$)).ti,ab.	2,426
8	exp *TRICYCLIC ANTIDEPRESSIVE AGENT/	45,029
9	(tricyclic$ adj2 (antidepress$ or anti-depress$ or drug$ or agent$ or med$)).ti,ab.	14,054
10	(Amitriptyline or Clomipramine or Desipramine or Dothiepin or Doxepin or Imipramine or Iprindole or Lofepramine or Nortriptyline or Opipramol or Protriptyline or Trimipramine).mp.	94,182
11	*SEROTONIN NORADRENALIN REUPTAKE INHIBITOR/	600
12	(Serotonin norepinephrine reuptake inhibitor? or Serotonin norepinephrine re uptake inhibitor?).ti,ab.	1,462
13	(serotonin noradrenaline reuptake inhibitor? or serotonin noradrenaline re uptake inhibitor?).ti,ab.	418
14	SNRI.ti,ab.	1,524
15	(duloxetine or mirtazapine or venlafaxine or Desvenlafaxine or Milnacipran or Levomilnacipran or Sibutramine).mp.	39,808
16	exp *LOCAL ANESTHETIC AGENT/	111,885
17	((local or conduction or block$ or topical) adj3 an?esthe$).ti,ab.	74,302
18	(Benzocaine or Benzyl Alcohol or Bupivacaine or Carticaine or Cocaine or Dibucaine or Diphenhydramine or Ethyl Chloride or Etidocaine or Lidocaine or Mepivacaine or Prilocaine or Procaine or Propoxycaine or Tetracaine or Tetrodotoxin or Trimecaine).mp.	257,793
19	*CAPSAICIN/	7,041
20	Capsaicin?.mp.	23,076
21	*N METHYL DEXTRO ASPARTIC ACID RECEPTOR BLOCKING AGENT/	4,055
22	((N-METHYL-D-ASPARTATE or NMDA) adj3 (block$ or antagon$)).ti,ab.	22,189
23	Ketamin?.mp.	41,964
24	exp *ANTICONVULSIVE AGENT/	163,807
25	(Anti convuls$ or anticonvuls$ or anti epilep$ or antiepilep$).ti,ab.	76,002
26	(Acetazolamide or Bromide? or Carbamazepine or Chlormethiazole or Clonazepam or Clorazepate Dipotassium or Diazepam or Dimethadione or Estazolam or Ethosuximide or Flunarizine or Lorazepam or Magnesium Sulfate or Medazepam or Mephenytoin or Mephobarbital or Meprobamate or Nitrazepam or Paraldehyde or Phenobarbital or Phenytoin or Primidone or Riluzole or Thiopental or Tiletamine or Trimethadione or Valproic Acid or Valproate or Topiramate or Vigabatrin or Gabapentin or Neurontin or Pregabalin or Lyrica or Tiagabine or Gabitril).mp.	490,158
27	exp *NERVE BLOCK/	19,804
28	(nerve? adj3 block$).ti,ab.	20,772
29	(chemical adj3 neurolys?s).ti,ab.	145
30	chemodenervation?.ti,ab.	513
31	exp *NERVOUS SYSTEM/ and exp *ABLATION THERAPY/	258
32	(nerve? adj3 ablat$).ti,ab.	1,185
33	exp *DENERVATION/	13,714
34	Denervation?.ti,ab.	30,967
35	or/5-34	1,046,550
36	4 and 35	531
37	limit 36 to english language	490
38	letter.pt. or LETTER/	1,095,318
39	note.pt.	775,951
40	editorial.pt.	634,717
41	CASE REPORT/ or CASE STUDY/	2,578,494
42	(letter or comment*).ti.	199,107

No.	Query	Results
43	or/38-42	4,873,409
44	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.	1,584,604
45	43 not 44	4,829,533
46	ANIMAL/ not HUMAN/	1,464,294
47	NONHUMAN/	5,984,520
48	exp ANIMAL EXPERIMENT/	2,468,336
49	exp EXPERIMENTAL ANIMAL/	676,936
50	ANIMAL MODEL/	1,276,806
51	exp RODENT/	3,921,449
52	(rat or rats or mouse or mice).ti.	1,640,666
53	or/45-52	13,234,017
54	37 not 53	362
55	limit 54 to yr="2016-2019" **[All populations 2016-2019]**	64
56	limit 54 to yr="2009-2015"	163
57	(extrapelvic or extra pelvic or extra genital or extragenital or (outside adj3 pelvi?) or (beyond adj3 pelvi?) or gastrointestin$ or intestin$ or urinary or bowel or colorectal or colon$ or diaphragm$ or endometrial implant$).ti,ab,kw.	2,008,961
58	56 AND 57 **[Extra pelvic population 2009-2015]**	45
59	menopause/ or postmenopause/ or (menopaus$ or postmenopaus$ or post-menopaus$).ti,ab,kw.	157,056
60	56 AND 59 **[Postmenopausal population 2009-2015]**	6
61	pregnancy/ or pregnant woman/ or pregnan$.ti,ab,kw.	1,012,616
62	56 AND 61 **[Pregnant population 2009-2015]**	22
63	(adenomyosis or adenomyoma? or adenometritis or adenomyositis or adenomyometritis).ti,ab,kw. or ADENOMYOSIS/	6,385
64	56 AND 63 NOT (58 OR 60 OR 62) **[Adenomyosis population 2009-2015]**	20

Pharmacological management – Hormonal medical treatments

Q7c. In people with endometriosis or adenomyosis, what is the effect of hormonal medical treatments on patient outcomes?

Table App 45 Hormonal medical treatments – MEDLINE search strings

No.	Query	Results
1	META-ANALYSIS/ or META-ANALYSIS AS TOPIC/ or (meta analy* or metanaly* or metaanaly*).ti,ab. or ((systematic* or evidence*) adj2 (review* or overview*)).ti,ab. or (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab. or (search strategy or search criteria or systematic search or study selection or data extraction).ab. or (search* adj4 literature).ab. or (Medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab. or cochrane.jw.	418,182
2	(randomized controlled trial or controlled clinical trial or pragmatic clinical trial).pt. or randomi#ed.ab. or placebo.ab. or randomly.ab. or CLINICAL TRIALS AS TOPIC/ or trial.ti.	1,278,570
3	1 or 2	1,590,947
4	ENDOMETRIOSIS/ or ADENOMYOSIS/ or (endometriosis or endometrioma? or adenomyos#s or adenomyoma? or adenometrit#s or adenomyosit#s or adenomyometrit#s).ti,ab.	28,488
5	CONTRACEPTION/ or OVULATION INHIBITION/ or exp CONTRACEPTIVE AGENTS, FEMALE/ or CONTRACEPTIVE DEVICES, FEMALE/ or exp INTRAUTERINE DEVICES/ or exp PROGESTERONE CONGENERS/ or exp ESTRADIOL CONGENERS/ or exp NORPREGNANES/ or exp PREGNANES/ or contracept$.ti,ab. or (estrogen? or oestrogen? or estradiol or ethinyl?estradiol or progest$ or levonorgestrel or norethisterone or norgestimate or desogestrel or drospirenone or gestodene or cyproterone acetate or mestranol or dienogest or nomegestrol acetate or norelgestromin or etonogestrel or medroxyprogesterone).mp. or (depo provera or noristerat or sayana press or nexplanon or mirena or jaydess or LNG-IUS).ti,ab. or (danazol or gestrinone).mp. or exp ESTROGEN RECEPTOR MODULATORS/ or HORMONE ANTAGONISTS/ or exp ESTROGEN ANTAGONISTS/ or CHORIONIC GONADOTROPIN/tu or exp GONADOTROPIN-RELEASING HORMONE/ or (gonadotrop?in$ or GnRH or Gn RH).mp. or (buserelin or goserelin or leuporelin).mp. or exp Gonadotropin-Releasing Hormone/ai or (((GnRH or Gn RH) adj3 antagonist?) or (gonadotropin releasing adj3 antagonist?) or etonorgestrel).ti,ab. or LUTEOLYTIC AGENTS/ or TAMOXIFEN/ or RALOXIFENE/ or MIFEPRISTONE/ or (SERM? or SPRM? or antiestrogen? or antioestrogen? or antiprogest$ or luteoly$).ti,ab. or (tamoxifen or raloxifene or ulipristal or mifepristone or RU 486).mp. or HORMONE REPLACEMENT THERAPY/ or ESTROGEN REPLACEMENT THERAPY/ or tibolone.mp. or (hormone adj	770,962

No.	Query	Results
	(replace$ or substitut$) adj therap$).ti,ab. or (HRT or "add back").ti,ab. or exp AROMATASE INHIBITORS/ or aromatase inhibit$.ti,ab. or (anastr#zole or lanastr#zole or exemestane or letr#zole).mp.	
6	and/3-5	1,023
7	*Endometriosis/dt or Adenomyosis/dt	1,783
8	and/3,7	555
9	or/6,8	1,125
10	limit 9 to english language	1,004
11	10 not ((LETTER/ or EDITORIAL/ or NEWS/ or exp HISTORICAL ARTICLE/ or ANECDOTES AS TOPIC/ or COMMENT/ or CASE REPORT/ or (letter or comment*).ti.) not (RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.))	989
12	11 not ((ANIMALS/ not HUMANS/) or exp ANIMALS, LABORATORY/ or exp ANIMAL EXPERIMENTATION/ or exp MODELS, ANIMAL/ or exp RODENTIA/ or (rat or rats or mouse or mice).ti.)	834
13	limit 12 to yr="2016-2019" **[All populations 2016-2019]**	151
14	(surgery or surgeries or surgical or operation$ or operative or post operat$ or postoperat$ or pre operat$ or preoperat$ or post surg$ or postsurg$ or pre surg$ or presurg$ or post laparoscop$ or postlaparoscop$ or pre laparoscop$ or prelaparoscop$).ti.	771,216
15	13 and 14 **[Hormonal Tx and surgery 2016-2019]**	14
16	13 not 15 **[Hormonal Tx 2016-2019]**	137
17	limit 12 to yr="2009-2015"	227
18	(extrapelvic or extra pelvic or extra genital or extragenital or (outside adj3 pelvi?) or (beyond adj3 pelvi?) or gastrointestin$ or intestin$ or urinary or bowel or colorectal or colon$ or diaphragm$ or endometrial implant$).ti,ab,kw.	1,412,634
19	17 and 18 **[Extra pelvic population 2009-2015]**	10
20	19 and 14 **[Hormonal Tx and surgery 2009-2015]**	3
21	19 not 20 **[Hormonal Tx 2009-2015]**	8
22	menopause/ or postmenopause/ or (menopaus$ or postmenopaus$ or post-menopaus$).ti,ab,kw.	97,879
23	(17 and 22) not 19 **[Postmenopausal population 2009-2015]**	20
24	23 and 14 **[Hormonal Tx and surgery 2009-2015]**	4
25	23 not 24 **[Hormonal Tx 2009-2015]**	16
26	Pregnancy/ or Pregnant Women/ or pregnan$.ti,ab,kw.	968,672
27	(17 and 26) not (19 or 23) **[Pregnant population 2009-2015]**	46
28	27 and 14 **[Hormonal Tx and surgery 2009-2015]**	10
29	27 not 28 **[Hormonal Tx 2009-2015]**	36
30	ADENOMYOSIS/ or (adenomyos#s or adenomyoma? or adenometrit#s or adenomyosit#s or adenomyometrit#s).ti,ab.	3,035
31	(17 and 30) not (19 or 23 or 27) **[Adenomyosis population 2009-2015]**	15
32	14 and 31 **[Hormonal Tx and surgery 2009-2015]**	0
33	31 not 32**[Hormonal Tx 2009-2015]**	15

Table App 46 Hormonal medical treatments – EMBASE search strings

No.	Query	Results
1	SYSTEMATIC REVIEW/ or META-ANALYSIS/ or (meta analy* or metanaly* or metaanaly*).ti,ab. or ((systematic or evidence) adj2 (review* or overview*)).ti,ab. or (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab. or (search strategy or search criteria or systematic search or study selection or data extraction).ab. or (search* adj4 literature).ab. or (Medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab. or ((pool* or combined) adj2 (data or trials or studies or results)).ab. or cochrane.jw.	617,532
2	(random* or factorial* or (crossover* or cross over*) or ((doubl* or singl*) adj blind*) or (assign* or allocat* or volunteer* or placebo*)).ti,ab. or CROSSOVER PROCEDURE/ or SINGLE BLIND PROCEDURE/ or RANDOMIZED CONTROLLED TRIAL/ or DOUBLE BLIND PROCEDURE/	2,269,058
3	1 or 2	2,701,649
4	ENDOMETRIOSIS/ or ADENOMYOSIS/ or (endometriosis or endometrioma? or adenomyos#s or adenomyoma? or adenometrit#s or adenomyosit#s or adenomyometrit#s).ti,ab.	46,665
5	CONTRACEPTION/ or OVULATION INHIBITION/ or exp CONTRACEPTIVE AGENT/ or exp FEMALE CONTRACEPTIVE DEVICE/ or exp GESTAGEN/ or exp PROGESTERONE DERIVATIVE/ or exp ESTRADIOL DERIVATIVE/ or PREGNANE DERIVATIVE/ or contracept$.ti,ab. or (estrogen? or oestrogen? or estradiol or ethinyl?estradiol or progest$ or	826,669

No.	Query	Results
	levonorgestrel or norethisterone or norgestimate or desogestrel or drospirenone or gestodene or cyproterone acetate or mestranol or dienogest or nomegestrol acetate or norelgestromin or etonogestrel or medroxyprogesterone).mp. or (depo provera or noristerat or sayana press or nexplanon or mirena or jaydess or LNG-IUS).ti,ab. or SELECTIVE ESTROGEN RECEPTOR MODULATOR/ or PROGESTERONE RECEPTOR MODULATOR/ or HORMONE ANTAGONIST/ or ANTIESTROGEN/ or CHORIONIC GONADOTROPIN/dt or exp GONADORELIN DERIVATIVE/ or DANAZOL/ or GESTRINONE/ or (danazol or gestrinone).mp. or (gonadotrop?in$ or GnRH or Gn RH).mp. or (buserelin or goserelin or leuporelin).mp. or gonadorelin antagonist/ or (((GnRH or Gn RH) adj3 antagonist?) or (gonadotropin releasing adj3 antagonist?) or etonorgestrel).ti,ab. or TAMOXIFEN/ or RALOXIFENE/ or MIFEPRISTONE/ or ULIPRISTAL/ or (SERM? or SPRM? or antiestrogen? or antioestrogen? or antiprogest$ or luteoly$).ti,ab. or (tamoxifen or raloxifene or ulipristal or mifepristone or RU 486).mp. or exp HORMONE SUBSTITUTION/ or ESTROGEN THERAPY/ or TIBOLONE/ or tibolone.mp. or (hormone adj (replace$ or substitut$) adj therap$).ti,ab. or (HRT or "add back").ti,ab. or exp AROMATASE INHIBITOR/ or ANASTROZOLE/ or EXEMESTANE/ or LETROZOLE/ or aromatase inhibit$.ti,ab. or (anastr#zole or lanastr#zole or exemestane or letr#zole).mp.	
6	and/3-5	1,979
7	*ENDOMETRIOSIS/dt or exp adenomyosis/dt	3,902
8	3 and 7	809
9	6 or 8	2,108
10	limit 9 to english language	1,965
11	(letter.pt. or LETTER/ or note.pt. or editorial.pt. or CASE REPORT/ or CASE STUDY/ or (letter or comment*).ti.) not (RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.)	4,830,078
12	10 not (letter.pt. or LETTER/ or note.pt. or editorial.pt. or CASE REPORT/ or CASE STUDY/ or (letter or comment*).ti.) not (RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.)	628
13	12 not ((ANIMAL/ not HUMAN/) or NONHUMAN/ or exp ANIMAL EXPERIMENT/ or exp EXPERIMENTAL ANIMAL/ or ANIMAL MODEL/ or exp RODENT/ or (rat or rats or mouse or mice).ti.)	488
14	limit 13 to yr="2016-2019" **[All populations 2016-2019]**	144
15	(surgery or surgeries or surgical or operation$ or operative or post operat$ or postoperat$ or pre operat$ or preoperat$ or post surg$ or postsurg$ or pre surg$ or presurg$ or post laparoscop$ or postlaparoscop$ or pre laparoscop$ or prelaparoscop$).ti.	982,333
16	14 and 15 **[Hormonal Tx and surgery 2016-2019]**	6
17	14 not 16 **[Hormonal Tx 2016-2019]**	138
18	limit 13 to yr="2009-2015"	192
19	(extrapelvic or extra pelvic or extra genital or extragenital or (outside adj3 pelvi?) or (beyond adj3 pelvi?) or gastrointestin$ or intestin$ or urinary or bowel or colorectal or colon$ or diaphragm$ or endometrial implant$).ti,ab,kw.	2,009,208
20	18 and 19 **[Extra pelvic population 2009-2015]**	15
21	15 and 20 **[Hormonal Tx and surgery 2009-2015]**	1
22	20 not 21 **[Hormonal Tx 2009-2015]**	14
23	menopause/ or postmenopause/ or (menopaus$ or postmenopaus$ or post-menopaus$).ti,ab,kw.	157,097
24	(18 and 23) not 20 **[Postmenopausal population 2009-2015]**	12
25	15 and 24 **[Hormonal Tx and surgery 2009-2015]**	0
26	24 not 25 **[Hormonal Tx 2009-2015]**	12
27	pregnancy/ or pregnant woman/ or pregnan$.ti,ab,kw.	1,013,166
28	(18 and 27) not (20 or 24) **[Pregnant population 2009-2015]**	36
29	15 and 28 **[Hormonal Tx and surgery 2009-2015]**	0
30	28 not 29 **[Hormonal Tx 2009-2015]**	36
31	ADENOMYOSIS/ or (adenomyos#s or adenomyoma? or adenometrit#s or adenomyosit#s or adenomyometrit#s).ti,ab.	6,295
32	(18 and 31) not (20 or 24 or 28) **[Adenomyosis population 2009-2015]**	21
33	15 and 32 **[Hormonal Tx and surgery 2009-2015]**	0
34	32 not 33 **[Hormonal Tx 2009-2015]**	21

Alternatives to pharmacological and surgical management

Q8. In people with endometriosis or adenomyosis, what alternatives to pharmacological and surgical management are effective for managing endometriosis- or adenomyosis-associated pain?

Table App 47 Alternative to pharmacological and surgical management – MEDLINE search strings

No.	Query	Results
1	META-ANALYSIS/	105,818
2	META-ANALYSIS AS TOPIC/	17,279
3	(meta analy* or metanaly* or metaanaly*).ti,ab.	157,194
4	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.	188,559
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.	41,335
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.	50,556
7	(search* adj4 literature).ab.	60,201
8	(Medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.	209,350
9	cochrane.jw.	14,623
10	or/1-9	417,845
11	randomized controlled trial.pt.	491,376
12	controlled clinical trial.pt.	93,315
13	pragmatic clinical trial.pt.	1,178
14	randomi#ed.ab.	546,855
15	placebo.ab.	201,518
16	randomly.ab.	319,667
17	CLINICAL TRIALS AS TOPIC/	188,692
18	trial.ti.	206,068
19	or/11-18	1,278,092
20	or/10,19	1,590,213
21	ENDOMETRIOSIS/	21,088
22	ADENOMYOSIS/	653
23	(endometriosis or endometrioma? or adenomyos#s or adenomyoma? or adenometrit#s or adenomyosit#s or adenomyometrit#s).ti,ab.	25,085
24	or/21-23	28,480
25	((non-med$ or nonmed$ or non-pharm$ or nonpharm$) adj3 (therap$ or manag$ or treat$)).ti,ab.	8,665
26	BEHAVIORAL MEDICINE/	1,443
27	exp PSYCHOTHERAPY/	189,706
28	exp PHYSICAL THERAPY MODALITIES/	146,438
29	((behavi$ or cognit$) adj3 (technique? or therap$ or psychotherap$)).ti,ab.	35,547
30	(psychotherap$ or psycho therap$ or logotherap$ or logo therap$).ti,ab.	40,648
31	(physiotherap$ or kinesiotherap$).ti,ab.	24,099
32	((physio or physical or kinesio or manual or exercise) adj1 therap$).ti,ab.	27,242
33	CBT.ti,ab.	9,830
34	(mindfulness or mind-body or relax$ or meditat$ or cope? or coping).ti,ab.	249,316
35	PAIN MANAGEMENT/	31,644
36	PAIN/rh [Rehabilitation]	1,356
37	CHRONIC PAIN/rh, th [Rehabilitation, Therapy]	3,762
38	exp PELVIC PAIN/rh, th [Rehabilitation, Therapy]	1,734
39	pain management.ti,ab.	21,784
40	SELF CARE/ or PATIENT PARTICIPATION/ or PEER GROUP/ or SOCIAL SUPPORT/	137,204
41	expert patient?.ti,ab.	238
42	((peer or social) adj3 support$).ti,ab.	45,547
43	support group?.ti,ab.	6,869
44	exp EXERCISE THERAPY/ or exp EXERCISE/	214,151
45	(exercis$ or yoga or pilates or tai ji or tai chi).ti,ab.	282,995
46	HYPNOSIS/ or exp HYPNOSIS, ANESTHETIC/	9,802

No.	Query	Results
47	(hypno$ or mesmeris$).ti,ab.	21,729
48	SEX COUNSELING/	882
49	((sex$ or psychosex$) adj3 (counsel$ or therap$)).ti,ab.	4,634
50	exp BIOFEEDBACK, PSYCHOLOGY/	10,637
51	(biofeedback or bio feedback or bio feed back or psychophysiolog$).ti,ab.	15,704
52	exp COMPLEMENTARY THERAPIES/	220,810
53	exp TRADITIONAL MEDICINE/	37,362
54	((alternative or compl#ment$ or herb$ or Chinese or Oriental or traditional or non-Western or nonWestern or African or Arabic or Indian or Hindu or Ayurvedic or Asian or folk or holistic) adj (medicine? or therap$ or remed$)).ti,ab.	84,166
55	(Ayurveda or Shaman$).ti,ab.	2,485
56	ACUPUNCTURE/	1,632
57	(acupuncture or electroacupuncture or acupoint? or meridian? or mox#bust$ or acu$ point? or needling or shu).ti,ab.	31,146
58	exp TRANSCUTANEOUS ELECTRIC NERVE STIMULATION/	8,174
59	((cutaneous or transcutaneous or percutaneous or dermal or transdermal) adj2 (nerve stimulat$ or electrostimulat$ or electro stimulat$)).ti,ab.	2,964
60	(electroanalges$ or electro analges$ or TENS).ti,ab.	14,997
61	exp THERAPY, SOFT TISSUE/	6,746
62	(manipulat$ adj1 (therap$ or medicine or treatment?)).ti,ab.	3,182
63	(massag$ or acupressure or shiatsu or tui na).ti,ab.	11,074
64	MANIPULATION, OSTEOPATHIC/	988
65	osteopath$.ti,ab.	5,260
66	MANIPULATION, CHIROPRACTIC/	963
67	chiropra$.ti,ab.	5,628
68	reflexolog$.ti,ab.	552
69	DRUGS, CHINESE HERBAL/ or HERBAL MEDICINE/ or exp PLANT EXTRACTS/ or PLANTS, MEDICINAL/	202,224
70	(phytotherap$ or phytopharma$).ti,ab.	2,516
71	plant extract?.ti,ab.	9,434
72	NATUROPATHY/	983
73	naturopath$.ti,ab.	1,023
74	HOMEOPATHY/	4,699
75	(homeopath$ or homeotherap$).ti,ab.	4,442
76	exp DIET THERAPY/ or DIET/	201,043
77	(diet$ adj2 (restrict$ or low carb$ or low protein or low fat or gluten free or vegetarian or vegan or raw food or paleo$ or endo$)).ti,ab.	30,760
78	endodiet$.ti,ab.	-0
79	or/25-78	1,719,318
80	and/24,79	957
81	limit 80 to english language	783
82	LETTER/	1,046,012
83	EDITORIAL/	504,717
84	NEWS/	197,536
85	exp HISTORICAL ARTICLE/	391,354
86	ANECDOTES AS TOPIC/	4,732
87	COMMENT/	807,916
88	CASE REPORT/	2,049,714
89	(letter or comment*).ti.	143,661
90	or/82-89	4,224,419
91	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.	1,200,635
92	90 not 91	4,199,553
93	ANIMALS/ not HUMANS/	4,594,539

No.	Query	Results
94	exp ANIMALS, LABORATORY/	851,769
95	exp ANIMAL EXPERIMENTATION/	9,176
96	exp MODELS, ANIMAL/	547,052
97	exp RODENTIA/	3,153,032
98	(rat or rats or mouse or mice).ti.	1,305,359
99	or/92-98	9,543,783
100	81 not 99	629
101	and/20,100	155
102	limit 101 to yr="2016-2019" **[All populations 2016-2019]**	43
103	limit 101 to yr="2009-2015"	58
104	(extrapelvic or extra pelvic or extra genital or extragenital or (outside adj3 pelvi?) or (beyond adj3 pelvi?) or gastrointestin$ or intestin$ or urinary or bowel or colorectal or colon$ or diaphragm$ or endometrial implant).ti,ab,kw.	1,412,131
105	103 AND 104 **[Extra pelvic population 2009-2015]**	6
106	menopause/ or postmenopause/ or (menopaus$ or postmenopaus$ or post-menopaus$).ti,ab,kw.	97,860
107	103 AND 106 NOT 105 **[Postmenopausal population 2009-2015]**	6
108	Pregnancy/ or Pregnant Women/ or pregnan$.ti,ab,kw.	968,482
109	103 AND 108 NOT (105 OR 107) **[Pregnant population 2009-2015]**	12
110	(adenomyosis or adenomyoma? or adenometritis or adenomyositis or adenomyometritis).ti,ab,kw. or ADENOMYOSIS/	3,063
111	103 AND 110 NOT (105 OR 107 OR 109) **[Adenomyosis population 2009-2015]**	2
112	Tai Ji/ OR Meditation/ OR Medicine, Ayurvedic/ OR Aromatherapy/ OR Dietary Supplements/ OR (tai chi or tai ji or taichi or taiji or meditation? or ayurveda or Shaman$ or ayurvedic or dietary suppl$).ti,ab,kw.	78,073
113	(112 AND 20 AND 24) NOT (99 OR 102 OR 105 OR 107 OR 109 OR 111)	9
114	limit 113 to yr="2009-2019"	8
115	limit 114 to english language **[Extra interventions 2009-2019]**	7

Table App 48 Alternatives to pharmacological and surgical management – EMBASE search strings

No.	Query	Results
1	SYSTEMATIC REVIEW/	222,884
2	META-ANALYSIS/	173,688
3	(meta analy* or metanaly* or metaanaly*).ti,ab.	209,389
4	((systematic or evidence) adj2 (review* or overview*)).ti,ab.	229,008
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.	54,608
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.	61,158
7	(search* adj4 literature).ab.	77,738
8	(Medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.	259,910
9	((pool* or combined) adj2 (data or trials or studies or results)).ab.	72,106
10	cochrane.jw.	20,818
11	or/1-10	617,302
12	random*.ti,ab.	1,481,703
13	factorial*.ti,ab.	36,966
14	(crossover* or cross over*).ti,ab.	104,214
15	((doubl* or singl*) adj blind*).ti,ab.	231,929
16	(assign* or allocat* or volunteer* or placebo*).ti,ab.	1,015,700
17	CROSSOVER PROCEDURE/	61,618
18	SINGLE BLIND PROCEDURE/	37,075
19	RANDOMIZED CONTROLLED TRIAL/	579,192
20	DOUBLE BLIND PROCEDURE/	170,011
21	or/12-20	2,268,666

No.	Query	Results
22	or/11,21	2,701,117
23	ENDOMETRIOSIS/	38,592
24	ADENOMYOSIS/	4,938
25	(endometriosis or endometrioma? or adenomyos#s or adenomyoma? or adenometrit#s or adenomyosit#s or adenomyometrit#s).ti,ab.	38,697
26	or/23-25	46,661
27	((non-med$ or nonmed$ or non-pharm$ or nonpharm$) adj3 (therap$ or manag$ or treat$)).ti,ab.	13,009
28	BEHAVIORAL MEDICINE/	1,913
29	exp PSYCHOTHERAPY/	265,429
30	exp PHYSIOTHERAPY/	92,949
31	((behavi$ or cognit$) adj3 (technique? or therap$ or psychotherap$)).ti,ab.	52,534
32	(psychotherap$ or psycho therap$ or logotherap$ or logo therap$).ti,ab.	64,693
33	(physiotherap$ or kinesiotherap$).ti,ab.	47,017
34	((physio or physical or kinesio or manual or exercise) adj1 therap$).ti,ab.	43,235
35	CBT.ti,ab.	15,171
36	(mindfulness or mind-body or relax$ or meditat$ or cope? or coping).ti,ab.	304,593
37	PAIN/rh, th [Rehabilitation, Therapy]	10,926
38	CHRONIC PAIN/rh, th [Rehabilitation, Therapy]	7,668
39	exp PELVIC PAIN/rh, th [Rehabilitation, Therapy]	1,225
40	DYSMENORRHEA/rh, th [Rehabilitation, Therapy]	731
41	pain management.ti,ab.	33,168
42	SELF CARE/ or PATIENT PARTICIPATION/ or PEER GROUP/ or SOCIAL SUPPORT/	182,483
43	expert patient?.ti,ab.	442
44	((peer or social) adj3 support$).ti,ab.	58,478
45	support group?.ti,ab.	10,650
46	exp KINESIOTHERAPY/	79,410
47	(exercis$ or yoga or pilates or tai ji or tai chi).ti,ab.	400,686
48	HYPNOSIS/	16,676
49	(hypno$ or mesmeris$).ti,ab.	30,944
50	SEX COUNSELING/	1,336
51	((sex$ or psychosex$) adj3 (counsel$ or therap$)).ti,ab.	7,335
52	exp FEEDBACK SYSTEM/ or exp PSYCHOPHYSIOLOGY/	1,084,755
53	(biofeedback or bio feedback or bio feed back or psychophysiolog$).ti,ab.	23,173
54	exp ALTERNATIVE MEDICINE/	49,211
55	exp TRADITIONAL MEDICINE/	87,396
56	((alternative or compl#ment$ or herb$ or Chinese or Oriental or traditional or non-Western or nonWestern or African or Arabic or Indian or Hindu or Ayurvedic or Asian or herbal or folk or holistic) adj (medicine? or therap$ or remed$)).ti,ab.	121,949
57	(Ayurveda or Shaman$).ti,ab.	4,300
58	(acupuncture or electroacupuncture or acupoint? or meridian? or mox#bust$ or acu$ point? or needling or shu).ti,ab.	43,504
59	TRANSCUTANEOUS NERVE STIMULATION/	6,738
60	((cutaneous or transcutaneous or percutaneous or dermal or transdermal) adj2 (nerve stimulat$ or electrostimulat$ or electro stimulat$)).ti,ab.	4,252
61	(electroanalges$ or electro analges$ or TENS).ti,ab.	15,853
62	exp ACUPRESSURE/ or MASSAGE/ or SOFT TISSUE THERAPY/	18,028
63	(manipulat$ adj1 (therap$ or medicine or treatment?)).ti,ab.	4,120
64	(massag$ or acupressure or shiatsu or tui na).ti,ab.	17,748
65	OSTEOPATHIC MEDICINE/	4,756
66	osteopath$.ti,ab.	7,548
67	CHIROPRACTIC/	4,647
68	chiropra$.ti,ab.	5,799

No.	Query	Results
69	REFLEXOLOGY/	745
70	reflexolog$.ti,ab.	818
71	HERBAL MEDICINE/ or exp PLANT EXTRACT/ or exp MEDICINAL PLANT/	381,065
72	(phytotherap$ or phytopharma$).ti,ab.	5,393
73	plant extract?.ti,ab.	15,719
74	naturopath$.ti,ab.	1,523
75	HOMEOPATHY/	9,638
76	(homeopath$ or homeotherap$).ti,ab.	6,680
77	exp DIET THERAPY/ or DIET/ or LOW CARBOHYDRATE DIET/ or exp VEGETARIAN DIET/ or RAW FOOD DIET/	587,273
78	(diet$ adj2 (restrict$ or low carb$ or low protein or low fat or gluten free or vegetarian or vegan or raw food or paleo$ or endo$)).ti,ab.	44,614
79	endodiet$.ti,ab.	0
80	or/27-79	3,333,338
81	and/26,80	2,429
82	limit 81 to english language	2,196
83	letter.pt. or LETTER/	1,095,318
84	note.pt.	775,951
85	editorial.pt.	634,717
86	CASE REPORT/ or CASE STUDY/	2,578,494
87	(letter or comment*).ti.	199,107
88	or/83-87	4,873,409
89	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.	1,584,604
90	88 not 89	4,829,533
91	ANIMAL/ not HUMAN/	1,464,294
92	NONHUMAN/	5,984,520
93	exp ANIMAL EXPERIMENT/	2,468,336
94	exp EXPERIMENTAL ANIMAL/	676,936
95	ANIMAL MODEL/	1,276,806
96	exp RODENT/	3,921,449
97	(rat or rats or mouse or mice).ti.	1,640,666
98	or/90-97	13,234,017
99	82 not 98	1,523
100	and/22,99	386
101	limit 100 to yr="2016-2019" **[All populations 2016-2019]**	139
102	limit 100 to yr="2009-2015"	178
103	(extrapelvic or extra pelvic or extra genital or extragenital or (outside adj3 pelvi?) or (beyond adj3 pelvi?) or gastrointestin$ or intestin$ or urinary or bowel or colorectal or colon$ or diaphragm$ or endometrial implant$).ti,ab,kw.	2,008,961
104	102 AND 103 **[Extra pelvic population 2009-2015]**	28
105	menopause/ or postmenopause/ or (menopaus$ or postmenopaus$ or post-menopaus$).ti,ab,kw.	157,056
106	102 AND 105 NOT 104 **[Postmenopausal population 2009-2015]**	20
107	pregnancy/ or pregnant woman/ or pregnan$.ti,ab,kw.	1,012,616
108	102 AND 107 NOT (104 OR 106) **[Pregnant population 2009-2015]**	29
109	(adenomyosis or adenomyoma? or adenometritis or adenomyositis or adenomyometritis).ti,ab,kw. or ADENOMYOSIS/	6,385
110	102 AND 109 NOT (104 OR 106 OR 108) **[Adenomyosis population 2009-2015]**	10
111	Tai chi/ OR Meditation/ OR Ayurveda/ OR ayurvedic drug/ OR Aromatherapy/ OR Dietary Supplement/ OR (tai chi or tai ji or taichi or taiji or meditation? or ayurveda or Shaman$ or ayurvedic or dietary suppl$).ti,ab,kw.	56,144
112	111 AND 22 AND 26 NOT (98 OR 101 OR 104 OR 106 OR 108 OR 110)	9
113	limit 112 to yr="2009-2019"	8
114	limit 113 to english language **[Extra interventions 2009-2019]**	7

Surgical management – Including ablation and excision

Q9a. In people with endometriosis or adenomyosis, what is the effect of surgical treatment on patient outcomes?

Table App 49 Surgical management – MEDLINE search strings

No.	Query	Results
1	META-ANALYSIS/ or META-ANALYSIS AS TOPIC/ or (meta analy* or metanaly* or metaanaly*).ti,ab. or ((systematic* or evidence*) adj2 (review* or overview*)).ti,ab. or (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab. or (search strategy or search criteria or systematic search or study selection or data extraction).ab. or (search* adj4 literature).ab. or (Medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab. or cochrane.jw.	418,182
2	(randomized controlled trial or controlled clinical trial or pragmatic clinical trial).pt. or randomi#ed.ab. or placebo.ab. or randomly.ab. or CLINICAL TRIALS AS TOPIC/ or trial.ti.	1,278,570
3	ENDOMETRIOSIS/ or ADENOMYOSIS/ or (endometriosis or endometrioma? or adenomyos#s or adenomyoma? or adenometrit#s or adenomyosit#s or adenomyometrit#s).ti,ab.	28,488
4	MINIMALLY INVASIVE SURGICAL PROCEDURES/ or LAPAROSCOPES/ or LAPAROTOMY/ or GYNECOLOGIC SURGICAL PROCEDURES/ or exp ABLATION TECHNIQUES/ or exp DIATHERMY/ or exp ULTRASONIC SURGICAL PROCEDURES/ or exp DRAINAGE/ or CYSTECTOMY/ or exp COLECTOMY/ or CYSTS/su or OVARIAN CYSTS/su or ((laparo$ or endoscop$ or peritoneo$ or telescop$ or keyhole$) adj3 (surg$ or ablat$ or excis$)).ti,ab. or (laparot$ or minilaparot$).ti,ab. or (minimal adj3 (surg$ or invasive or access)).ti,ab.	370,761
5	3 and 4	3,878
6	((*ENDOMETRIOSIS/ or ADENOMYOSIS/) and *LAPAROSCOPY/) or ((endometriosis or endometrioma? or adenomyos#s or adenomyoma? or adenometrit#s or adenomyosit#s or adenomyometrit#s) adj3 (excis$ or ablat$ or cystectom$ or shav$ or skin$ or resect$ or la#er$ or la#eroscop$ or videola#eroscop$ or electrosurg$ or electrocaut$ or caut$ or coagulat$ or electrocoagulat$ or thermocoagulat$ or vapo?ris$ or strip$ or diatherm$ or fulgurat$ or drain$ or fenestrat$ or aspirat$ or colpectom$ or colectom$)).ti,ab. or ENDOMETRIOSIS/su or ADENOMYOSIS/su	5,508
7	5 or 6	7,188
8	limit 7 to english language	5,875
9	8 not ((LETTER/ or EDITORIAL/ or NEWS/ or exp HISTORICAL ARTICLE/ or ANECDOTES AS TOPIC/ or COMMENT/ or CASE REPORT/ or (letter or comment*).ti.) not (RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.))	4,094
10	9 not ((ANIMALS/ not HUMANS/) or exp ANIMALS, LABORATORY/ or exp ANIMAL EXPERIMENTATION/ or exp MODELS, ANIMAL/ or exp RODENTIA/ or (rat or rats or mouse or mice).ti.)	3,949
11	10 and (1 or 2)	537
12	limit 11 to yr="2016-2019" **[All populations 2016-2019]**	117
13	limit 11 to yr="2009-2015"	203
14	(extrapelvic or extra pelvic or extra genital or extragenital or (outside adj3 pelvi?) or (beyond adj3 pelvi?) or gastrointestin$ or intestin$ or urinary or bowel or colorectal or colon$ or diaphragm$ or endometrial implant).ti,ab,kw.	1,412,634
15	13 and 14 **[Extra pelvic population 2009-2015]**	41
16	menopause/ or postmenopause/ or (menopaus$ or postmenopaus$ or post-menopaus$).ti,ab,kw.	97,879
17	(13 and 16) not 15 **[Postmenopausal population 2009-2015]**	4
18	Pregnancy/ or Pregnant Women/ or pregnan$.ti,ab,kw.	968,672
19	(13 and 18) not (15 or 17) **[Pregnant population 2009-2015]**	45
20	ADENOMYOSIS/ or (adenomyos#s or adenomyoma? or adenometrit#s or adenomyosit#s or adenomyometrit#s).ti,ab.	3,035
21	(13 and 20) not (15 or 17 or 19) **[Adenomyosis population 2009-2015]**	9

Table App 50 Surgical management – EMBASE search strings

No.	Query	Results
1	SYSTEMATIC REVIEW/ or META-ANALYSIS/ or (meta analy* or metanaly* or metaanaly*).ti,ab. or ((systematic or evidence) adj2 (review* or overview*)).ti,ab. or (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab. or (search strategy or search criteria or systematic search or study selection or data extraction).ab. or (search* adj4 literature).ab. or (Medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab. or ((pool* or combined) adj2 (data or trials or studies or results)).ab. or cochrane.jw.	617,532
2	(random* or factorial* or (crossover* or cross over*) or ((doubl* or singl*) adj blind*) or (assign* or allocat* or volunteer* or placebo*)).ti,ab. or CROSSOVER PROCEDURE/ or SINGLE BLIND PROCEDURE/ or RANDOMIZED CONTROLLED TRIAL/ or DOUBLE BLIND PROCEDURE/	2,269,058

No.	Query	Results
3	*ENDOMETRIOSIS/ or ADENOMYOSIS/ or (endometriosis or endometrioma? or adenomyos#s or adenomyoma? or adenometrit#s or adenomyosit#s or adenomyometrit#s).ti,ab.	41,437
4	*MINIMALLY INVASIVE SURGERY/ or *LAPAROSCOPE/ or *LAPAROTOMY/ or *GYNECOLOGIC SURGERY/ or *ABLATION THERAPY/ or *DIATHERMY/ or exp *ULTRASOUND SURGERY/ or *SURGICAL DRAINAGE/ or *CYSTECTOMY/ or exp *COLON RESECTION/ or CYST/su or OVARY CYST/su or VAGINAL CYST/su or ((laparo$ or endoscop$ or peritoneo$ or telescop$ or keyhole$) adj3 (surg$ or ablat$ or excis$)).ti,ab. or (laparot$ or minilaparot$).ti,ab.	211,900
5	3 and 4	5,466
6	((*ENDOMETRIOSIS/ or ADENOMYOSIS/) and *LAPAROSCOPY/) or ((endometriosis or endometrioma? or adenomyos#s or adenomyoma? or adenometrit#s or adenomyosit#s or adenomyometrit#s) adj3 (excis$ or ablat$ or cystectom$ or shav$ or skin$ or resect$ or la#er$ or la#eroscop$ or videola#eroscop$ or electrosurg$ or electrocaut$ or caut$ or coagulat$ or electrocoagulat$ or thermocoagulat$ or vapo?ris$ or strip$ or diatherm$ or fulgurat$ or drain$ or fenestrat$ or aspirat$ or colpectom$ or colectom$)).ti,ab. or *ENDOMETRIOSIS/su or ADENOMYOSIS/su	7,840
7	5 or 6	10,894
8	limit 7 to english language	9,402
9	8 not ((letter.pt. or LETTER/ or note.pt. or editorial.pt. or CASE REPORT/ or CASE STUDY/ or (letter or comment*).ti.) not (RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.))	6,837
10	9 not ((ANIMAL/ not HUMAN/) or NONHUMAN/ or exp ANIMAL EXPERIMENT/ or exp EXPERIMENTAL ANIMAL/ or ANIMAL MODEL/ or exp RODENT/ or (rat or rats or mouse or mice).ti.)	6,489
11	10 and (1 or 2)	941
12	limit 11 to yr="2016-2019"**[All populations 2016-2019]**	247
13	1 and 12 " **[SRs]**	117
14	12 not 13 **[RCTs]**	130
15	limit 11 to yr="2009-2015"	421
16	(extrapelvic or extra pelvic or extra genital or extragenital or (outside adj3 pelvi?) or (beyond adj3 pelvi?) or gastrointestin$ or intestin$ or urinary or bowel or colorectal or colon$ or diaphragm$ or endometrial implant$).ti,ab,kw.	2,009,208
17	15 and 16 **[Extra pelvic population 2009-2015]**	105
18	menopause/ or postmenopause/ or (menopaus$ or postmenopaus$ or post-menopaus$).ti,ab,kw.	157,070
19	(15 and 18) not 17 **[Postmenopausal population 2009-2015]**	14
20	pregnancy/ or pregnant woman/ or pregnan$.ti,ab,kw.	1,012,975
21	(15 and 20) not (17 or 19) **[Pregnant population 2009-2015]**	79
22	ADENOMYOSIS/ or (adenomyos#s or adenomyoma? or adenometrit#s or adenomyosit#s or adenomyometrit#s).ti,ab.	6292
23	(15 and 22) not (17 or 19 or 21) **[Adenomyosis population 2009-2015]**	37

Surgical management – Combination of surgery and hormonal treatment

Q9b. In people with endometriosis or adenomyosis, do hormonal medical treatments before or after surgery improve patient outcomes?

A separate search was not performed for this question. Any relevant evidence identified in searches for Q7c and Q9a were included under this question.

Surgical management – Hysterectomy

Q9c. In people with endometriosis or adenomyosis, what is the effect of hysterectomy on patient outcomes?

Table App 51 Hysterectomy – MEDLINE search strings

No.	Query	Results
1	ENDOMETRIOSIS/ or (endometriosis or endometrioma?).ti,ab.	27,050
2	HYSTERECTOMY/ or HYSTERECTOMY, VAGINAL/ or Hysterectom$.ab,ti. or (uter$ adj5 (excis$ or remov$)).ab,ti. or colpohysterectom$.ab,ti.	48,419
3	1 and 2	1,960
4	OVARIECTOMY/ or ovariectom$.ab,ti. or oophorectom$.ab,ti. or ((ovary or ovaries) adj5 (excis$ or remov$)).ab,ti.	44,616
5	3 and 4	504
6	limit 5 to english language	459

No.	Query	Results
7	6 not ((LETTER/ or EDITORIAL/ or NEWS/ or exp HISTORICAL ARTICLE/ or ANECDOTES AS TOPIC/ or COMMENT/ or CASE REPORT/ or (letter or comment*).ti.) not (RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.))	236
8	7 not ((ANIMALS/ not HUMANS/) or exp ANIMALS, LABORATORY/ or exp ANIMAL EXPERIMENTATION/ or exp MODELS, ANIMAL/ or exp RODENTIA/ or (rat or rats or mouse or mice).ti.)	226
9	limit 8 to yr="2016-2019" **[All populations 2016-2019]**	36
10	ADENOMYOSIS/ or (adenomyos#s or adenomyoma? or adenometrit#s or adenomyosit#s or adenomyometrit#s).ti,ab.	3,035
11	(1 or 10) and 2	2,389
12	limit 11 to english language	2,067
13	12 not ((LETTER/ or EDITORIAL/ or NEWS/ or exp HISTORICAL ARTICLE/ or ANECDOTES AS TOPIC/ or COMMENT/ or CASE REPORT/ or (letter or comment*).ti.) not (RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.))	1,465
14	13 not ((ANIMALS/ not HUMANS/) or exp ANIMALS, LABORATORY/ or exp ANIMAL EXPERIMENTATION/ or exp MODELS, ANIMAL/ or exp RODENTIA/ or (rat or rats or mouse or mice).ti.)	1,418
15	limit 14 to yr="2009-2019"	649
16	15 not 9 **[Adenomyosis population 2009-2019]**	613
17	exp meta-analysis/ or meta-analysis.mp. or metaanalysis.mp. or systematic review.mp. or systematic literature review.mp. or pooled analysis.mp. or (exp review literature as topic/ and systematic.mp.)	266,009
18	Clinical trial/ or Randomized controlled trial/ or Random allocation/ or Double-blind method/ or Cross-over studies/ or (Randomi#ed controlled trial$ or randomi#ed trial$ or rct or random allocation or randomly allocated or allocated randomly or (allocat$ adj3 random) or single blind$ or double blind$ or (((treble or triple) adj blind$) or placebo$)).tw.	1,113,085
19	16 and 17 **[SRs]**	24
20	(16 and 18) not 19 **[RCTs]**	29
21	16 not (19 or 20) **[Other studies]**	560

Table App 52 Hysterectomy – EMBASE search strings

No.	Query	Results
1	*ENDOMETRIOSIS/ or (endometriosis or endometrioma?).ti,ab.	37,185
2	exp *HYSTERECTOMY/ or Hysterectom$.ti,ab. or (uter$ adj5 (excis$ or remov$)).ti,ab. or colpohysterectom$.ti,ab.	65,228
3	1 and 2	2,635
4	*OVARIECTOMY/ or ovariectom$.ti,ab. or oophorectom$.ti,ab. or ((ovary or ovaries) adj5 (excis$ or remov$)).ti,ab.	54,790
5	3 and 4	666
6	limit 5 to english language	619
7	6 not ((letter.pt. or LETTER/ or note.pt. or editorial.pt. or CASE REPORT/ or CASE STUDY/ or (letter or comment*).ti.) not (RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.))	369
8	7 not ((ANIMAL/ not HUMAN/) or NONHUMAN/ or exp ANIMAL EXPERIMENT/ or exp EXPERIMENTAL ANIMAL/ or ANIMAL MODEL/ or exp RODENT/ or (rat or rats or mouse or mice).ti.)	351
9	limit 6 to yr="2016-2019"	153
10	*ADENOMYOSIS/ or (adenomyos#s or adenomyoma? or adenometrit#s or adenomyosit#s or adenomyometrit#s).ti,ab.	5,098
11	(1 or 10) and 2	3,715
12	limit 11 to english language **[All populations 2016-2019]**	3,347
13	12 not ((letter.pt. or LETTER/ or note.pt. or editorial.pt. or CASE REPORT/ or CASE STUDY/ or (letter or comment*).ti.) not (RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.))	2,523
14	13 not ((ANIMAL/ not HUMAN/) or NONHUMAN/ or exp ANIMAL EXPERIMENT/ or exp EXPERIMENTAL ANIMAL/ or ANIMAL MODEL/ or exp RODENT/ or (rat or rats or mouse or mice).ti.)	2,435
15	limit 14 to yr="2009-2019"	1,692
16	15 not 9 **[Adenomyosis population 2009-2019]**	1,619
17	meta-analysis/ or meta-analysis.mp. or metaanalysis.mp. or systematic review/ or systematic review.mp. or systematic literature review.mp. or pooled analysis.mp.	433,322
18	clinical trial/ or randomized controlled trial/ or randomization/ or crossover procedure/ or (randomi#ed controlled trial$ or randomi#ed trial$ or rct or (allocat$ adj3 random$) or single blind$ or double blind$ or placebo$).tw.	1,671,042
19	16 and 17 **[SRs]**	56
20	(16 and 18) not 19 **[RCTs]**	83
21	16 not (19 or 20) **[Other studies]**	1,480

Management strategies to enhance fertility

Q10. In people with endometriosis with and without infertility, what is the effect of hormonal and surgical treatments on fertility?

A separate search was not performed for this question. Any relevant evidence identified in searches for Q7c, Q9a and Q9b was included under this question.

Follow up in people who are asymptomatic

Q11. In people with endometriosis who are asymptomatic, do follow-up interventions improve primary patient outcomes?

A separate search was not performed for this question. Any relevant evidence identified in searches for Q5 and Q9 was included under this question.

Secondary prevention of endometriosis

Q12. In people who have received treatment for endometriosis, what interventions prevent the recurrence of endometriosis symptoms and lesions?

A separate search was not performed for this question. Any relevant evidence identified in searches for Q7 and Q9 was included under this question.

Appendix D Citations for included studies

Number of identified studies by research question

Table App 53 Literature search output and included studies

Question #	Topic	Search output (unique records)	Screened at full text	Included studies[a]
Q1	Signs and Symptoms	1,375	80	0
Q2a	Information and support	340	6	0
Q3	Timing	393	9	0
Q5a	Diagnosis - endometriosis	1,221	298	35
Q5b	Diagnosis - adenomyosis	338	48	7
Q6	Staging systems	381	38	0
Q7a	Pharmacological management – Analgesics	417	15	0
Q7b	Pharmacological management – Neuromodulators	89	4	0
Q7c	Pharmacological management – Hormonal medical treatments	346	92	12
Q8	Alternatives to pharmacological and surgical management	184	37	13
Q9a	Surgical management – Including ablation and excision	367	23	23
Q9b	Combination surgery plus hormonal treatment	NA	NA	4
Q9c	Surgical management – Hysterectomy	783	122	5
Q10	Management strategies to enhance fertility	NA	NA	0
Q11	Follow-up	NA	NA	0
Q12	Secondary prevention	NA	NA	2

a Excludes broad systematic reviews of management of endometriosis.

Citations for included studies by research question

Q1 – Signs and symptoms

No new relevant studies were identified in the literature search.

Q2a – Information and support

No new relevant studies were identified in the literature search.

Q3 – Timing of diagnosis and intervention

No new relevant studies were identified in the literature search.

Q5a – Diagnosis of endometriosis

Table App 54 Citations of identified studies - diagnosis of endometriosis

Study ID	Citation
Agrawal 2018	Agrawal, S.,Tapmeier, T.,Rahmioglu, N.,Kirtley, S.,Zondervan, K.,Becker, C.. The miRNA Mirage: How Close Are We to Finding a Non-Invasive Diagnostic Biomarker in Endometriosis? A Systematic Review. International Journal of Molecular Sciences. 2018. 19:17
Alborzi 2018	Alborzi, S.,Rasekhi, A.,Shomali, Z.,Madadi, G.,Alborzi, M.,Kazemi, M.,Nohandani, A. H.. Diagnostic accuracy of magnetic resonance imaging, transvaginal, and transrectal ultrasonography in deep infiltrating endometriosis. Medicine (United States). 2018. 97:8(e9536)
Baggio 2016	Baggio, S.,Zecchin, A.,Pomini, P.,Zanconato, G.,Genna, M.,Motton, M.,Montemezzi, S.,Franchi, M.. The role of computed tomography colonography in detecting bowel involvement in women with deep infiltrating endometriosis: Comparison with clinical history, serum ca125, and transvaginal sonography. Journal of Computer Assisted Tomography. 2016. 40:886-891

Study ID	Citation
Barra 2018	Barra, F.,Scala, C.,Biscaldi, E.,Vellone, V. G.,Ceccaroni, M.,Terrone, C.,Ferrero, S.. Ureteral endometriosis: A systematic review of epidemiology, pathogenesis, diagnosis, treatment, risk of malignant transformation and fertility. Human Reproduction Update. 2018. 24:710-730
Berger 2019	Berger, J. P.,Rhemrev, J.,Smeets, M.,Henneman, O.,English, J.,Jansen, F. W.. Limited Added Value of Magnetic Resonance Imaging After Dynamic Transvaginal Ultrasound for Preoperative Staging of Endometriosis in Daily Practice: A Prospective Cohort Study. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine. 2019. 38:989-996
Biscaldi 2014	Biscaldi, E.,Ferrero, S.,Maggiore, U. L. R.,Remorgida, V.,Venturini, P. L.,Rollandi, G. A.. Multidetector computerized tomography enema versus magnetic resonance enema in the diagnosis of rectosigmoid endometriosis. European Journal of Radiology. 2014. 83:261-267
Biscaldi 2011	Biscaldi, E.,Ferrero, S.,Remorgida, V.,Rollandi, G. A.. MDCT enteroclysis urography with split-bolus technique provides information on ureteral involvement in patients with suspected bowel endometriosis. American Journal of Roentgenology. 2011. 196:W635-W640
Chen 2019	Chen, Y. H.,Wang, D. B.,Guo, C. S.. Accuracy of Physical Examination, Transvaginal Sonography, Magnetic Resonance Imaging, and Rectal Endoscopic Sonography for Preoperative Evaluation of Rectovaginal Endometriosis. Ultrasound Quarterly. 2019. 35:54-60
Ferrero 2019a	Ferrero, S.,Barra, F.,Stabilini, C.,Vellone, V. G.,Leone Roberti Maggiore, U.,Scala, C.. Does Bowel Preparation Improve the Performance of Rectal Water Contrast Transvaginal Ultrasonography in Diagnosing Rectosigmoid Endometriosis?. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine. 2019. 38:1017-1025
Ferrero 2019b	Ferrero, S.,Scala, C.,Stabilini, C.,Vellone, V. G.,Barra, F.,Leone Roberti Maggiore, U.. Transvaginal sonography with vs without bowel preparation in diagnosis of rectosigmoid endometriosis: prospective study. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2019. 53:402-409
Ferrero 2011	Ferrero, S.,Biscaldi, E.,Morotti, M.,Venturini, P. L.,Remorgida, V.,Rollandi, G. A.,Valenzano Menada, M.. Multidetector computerized tomography enteroclysis vs. rectal water contrast transvaginal ultrasonography in determining the presence and extent of bowel endometriosis. Ultrasound in Obstetrics & Gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2011. 37:603-613
Ferrero 2017	Ferrero, S.,Biscaldi, E.,Vellone, V. G.,Venturini, P. L.,Leone Roberti Maggiore, U.. Computed tomographic colonography vs rectal water- contrast transvaginal sonography in diagnosis of rectosigmoid endometriosis: a pilot study. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2017. 49:515-523
Gao 2019	Gao, Y., Shen, M., Ma, X., Li, J., Wang, B., Wang, J., Tian, J. Seven hormonal biomarkers for diagnosing endometriosis: Meta-analysis and adjusted indirect comparison of diagnostic test accuracy. Journal of Minimally Invasive Gynecology. 2019. 26:1026-1035
Guerriero 2018	Guerriero, S.,Saba, L.,Pascual, M. A.,Ajossa, S.,Rodriguez, I.,Mais, V.,Alcazar, J. L.. Transvaginal ultrasound vs magnetic resonance imaging for diagnosing deep infiltrating endometriosis: systematic review and meta-analysis. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2018. 51:586-595
Guerriero 2016	Guerriero, S.,Ajossa, S.,Orozco, R.,Perniciano, M.,Jurado, M.,Melis, G. B.,Alcazar, J. L.. Accuracy of transvaginal ultrasound for diagnosis of deep endometriosis in the rectosigmoid: systematic review and meta-analysis. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2016. 47:281-289
Hernandez Gutierrez 2019	Hernandez Gutierrez, A.,Spagnolo, E.,Hidalgo, P.,Lopez, A.,Zapardiel, I.,Rodriguez, R.. Magnetic resonance imaging versus transvaginal ultrasound for complete survey of the pelvic compartments among patients with deep infiltrating endometriosis. International Journal of Gynecology and Obstetrics. 2019. 146:380-385
Hirsch 2017	Hirsch, M.,Duffy, J. M. N.,Deguara, C. S.,Davis, C. J.,Khan, K. S.. Diagnostic accuracy of Cancer Antigen 125 (CA125) for endometriosis in symptomatic women: A multi-center study. European Journal of Obstetrics and Gynecology and Reproductive Biology. 2017. 210:102-107
Hudelist 2011	Hudelist, G.,Ballard, K.,English, J.,Wright, J.,Banerjee, S.,Mastoroudes, H.,Thomas, A.,Singer, C. F.,Keckstein, J.. Transvaginal sonography vs. clinical examination in the preoperative diagnosis of deep infiltrating endometriosis. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2011. 37:480-487
Iosca 2013	Iosca, S.,Lumia, D.,Bracchi, E.,Duka, E.,De Bon, M.,Lekaj, M.,Uccella, S.,Ghezzi, F.,Fugazzola, C.. Multislice computed tomography with colon water distension (MSCT-c) in the study of intestinal and ureteral endometriosis. Clinical Imaging. 2013. 37:1061-1068
Jiang 2017	Jiang, J.,Liu, Y.,Wang, K.,Wu, X.,Tang, Y.. Rectal water contrast transvaginal ultrasound versus double-contrast barium enema in the diagnosis of bowel endometriosis. BMJ Open. 2017. 7:e017216
Kiesel 2019	Kiesel, L.,Sourouni, M.. Diagnosis of endometriosis in the 21st century. Climacteric. 2019. 22:296-302
Leone Roberti Maggiore 2017a	Leone Roberti Maggiore, U.,Biscaldi, E.,Vellone, V. G.,Venturini, P. L.,Ferrero, S.. Magnetic resonance enema vs rectal water-contrast transvaginal sonography in diagnosis of rectosigmoid endometriosis. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2017. 49:524-532
Leone Roberti Maggiore 2017b	Leone Roberti Maggiore, U.,Ferrero, S.,Candiani, M.,Somigliana, E.,Vigano, P.,Vercellini, P.. Bladder Endometriosis: A Systematic Review of Pathogenesis, Diagnosis, Treatment, Impact on Fertility, and Risk of Malignant Transformation [figure presented]. European Urology. 2017. 71:790-807

Study ID	Citation
Li 2018	Li, R.,Qiu, Y.. Diagnostic value of serum ICAM-1 for endometriosis: A meta-analysis. Medicine. 2018. 97:e11760
Mehedintu 2018	Mehedintu, C.,Brinduse, L. A.,Bratila, E.,Monroc, M.,Lemercier, E.,Suaud, O.,Collet-Savoye, C.,Roman, H.. Does Computed Tomography-Based Virtual Colonoscopy Improve the Accuracy of Preoperative Assessment Based on Magnetic Resonance Imaging in Women Managed for Colorectal Endometriosis?. Journal of Minimally Invasive Gynecology. 2018. 25:1009-1017
Moga 2019	Moga, M. A.,Balan, A.,Dimienescu, O. G.,Burtea, V.,Dragomir, R. M.,Anastasiu, C. V.. Circulating miRNAs as biomarkers for endometriosis and endometriosis-related ovarian cancer- an overview. Journal of Clinical Medicine. 2019. 8(5): doi:10.3390
Moura 2019b	Moura, A. P. C.,Ribeiro, H. S. A. A.,Bernardo, W. M.,Simoes, R.,Torres, U. S.,D'Ippolito, G.,Bazot, M.,Ribeiro, P. A. A. G.. Accuracy of transvaginal sonography versus magnetic resonance imaging in the diagnosis of rectosigmoid endometriosis: Systematic review and meta-analysis. PLoS ONE. 2019. 14(4): e0214842
Reid 2018	Reid, S.,Espada, M.,Lu, C.,Condous, G.. To determine the optimal ultrasonographic screening method for rectal/rectosigmoid deep endometriosis: Ultrasound "sliding sign," transvaginal ultrasound direct visualization or both?. Acta Obstetricia et Gynecologica Scandinavica. 2018. 97:1287-1292
Ros 2017	Ros, C.,Martinez-Serrano, M. J.,Rius, M.,Abrao, M. S.,Munros, J.,Martinez-Zamora, M. A.,Gracia, M.,Carmona, F.. Bowel Preparation Improves the Accuracy of Transvaginal Ultrasound in the Diagnosis of Rectosigmoid Deep Infiltrating Endometriosis: A Prospective Study. Journal of Minimally Invasive Gynecology. 2017. 24:1145-1151
Rosefort 2019	Rosefort, A.,Huchon, C.,Estrade, S.,Paternostre, A.,Bernard, J. P.,Fauconnier, A.. Is training sufficient for ultrasound operators to diagnose deep infiltrating endometriosis and bowel involvement by transvaginal ultrasound?. Journal of Gynecology Obstetrics and Human Reproduction. 2019. 48:109-114
Stabile Ianora 2013	Stabile Ianora, A. A.,Moschetta, M.,Lorusso, F.,Lattarulo, S.,Telegrafo, M.,Rella, L.,Scardapane, A.. Rectosigmoid endometriosis: Comparison between CT water enema and video laparoscopy. Clinical Radiology. 2013. 68:895-901
Woo 2019	Woo, S.,Suh, C. H.,Kim, H.. Diagnostic performance of computed tomography for bowel endometriosis: A systematic review and meta-analysis. European Journal of Radiology. 2019. 119:108638
Yap 2018	Yap, S. Z. L.,Leathersich, S.,Lu, J.,Fender, L.,Lo, G.. Pelvic MRI staging of endometriosis at 3T without patient preparation or anti-peristaltic: Diagnostic performance outcomes. European Journal of Radiology. 2018. 105:72-80
Young 2017	Young, S. W.,Dahiya, N.,Patel, M. D.,Abrao, M. S.,Magrina, J. F.,Temkit, M.,Kho, R. M.. Initial Accuracy of and Learning Curve for Transvaginal Ultrasound with Bowel Preparation for Deep Endometriosis in a US Tertiary Care Center. Journal of Minimally Invasive Gynecology. 2017. 24:1170-1176
Zannoni 2017	Zannoni, L.,Del Forno, S.,Coppola, F.,Papadopoulos, D.,Valerio, D.,Golfieri, R.,Caprara, G.,Paradisi, R.,Seracchioli, R.. Comparison of transvaginal sonography and computed tomography-colonography with contrast media and urographic phase for diagnosing deep infiltrating endometriosis of the posterior compartment of the pelvis: a pilot study. Japanese Journal of Radiology. 2017. 35:546-554

Q5b – Diagnosis of adenomyosis

Table App 55 Citations of included studies - diagnosis of adenomyosis

Study ID	Citation
Acar 2106	Acar, S.,Millar, E.,Mitkova, M.,Mitkov, V.. Value of ultrasound shear wave elastography in the diagnosis of adenomyosis. Ultrasound. 2016. 24:205-213
Andres 2018	Andres, M. P.,Borrelli, G. M.,Ribeiro, J.,Baracat, E. C.,Abrao, M. S.,Kho, R. M.. Transvaginal Ultrasound for the Diagnosis of Adenomyosis: Systematic Review and Meta-Analysis. Journal of Minimally Invasive Gynecology. 2018. 25:257-264
Bazot 2018	Bazot, M.,Darai, E.. Role of transvaginal sonography and magnetic resonance imaging in the diagnosis of uterine adenomyosis. Fertility and Sterility. 2018. 109:389-397
Champaneria 2010	Champaneria, R.,Abedin, P.,Daniels, J.,Balogun, M.,Khan, K. S.. Ultrasound scan and magnetic resonance imaging for the diagnosis of adenomyosis: systematic review comparing test accuracy. Acta Obstetricia et Gynecologica Scandinavica. 2010. 89:1374-84
Dakhly 2016	Dakhly, D. M. R.,Abdel Moety, G. A. F.,Saber, W.,Gad Allah, S. H.,Hashem, A. T.,Abdel Salam, L. O. E.. Accuracy of Hysteroscopic Endomyometrial Biopsy in Diagnosis of Adenomyosis. Journal of Minimally Invasive Gynecology. 2016. 23:364-371
Maheshwari 2012	Maheshwari, A.,Gurunath, S.,Fatima, F.,Bhattacharya, S.. Adenomyosis and subfertility: A systematic review of prevalence, diagnosis, treatment and fertility outcomes. Human Reproduction Update. 2012. 18:374-392
Meredith 2009	Meredith, S. M.,Sanchez-Ramos, L.,Kaunitz, A. M.. Diagnostic accuracy of transvaginal sonography for the diagnosis of adenomyosis: systematic review and metaanalysis. American Journal of Obstetrics and Gynecology. 2009. 201:e1-6

Q6 – Systems that can guide treatment

No new relevant studies were identified in the literature search.

Q7a – Pharmacological management – Analgesics

No new relevant studies were identified in the literature search.

Q7b – Pharmacological management – Neuromodulators

No new relevant studies were identified in the literature search.

Q7c – Pharmacological management – Hormonal medical treatments

Table App 56 Citations of included studies – hormonal medical treatments

Study ID	Citation
Abdou 2018	Abdou, A. M.,Ammar, I. M. M.,Alnemr, A. A. A.,Abdelrhman, A. A.. Dienogest Versus Leuprolide Acetate for Recurrent Pelvic Pain Following Laparoscopic Treatment of Endometriosis. Journal of Obstetrics & Gynaecology of India. 2018. 68:306-313
Carvalho 2018	Carvalho, N.,Margatho, D.,Cursino, K.,Benetti-Pinto, C. L.,Bahamondes, L.. Control of endometriosis-associated pain with etonogestrel-releasing contraceptive implant and 52-mg levonorgestrel-releasing intrauterine system: randomized clinical trial. Fertility & Sterility. 2018. 110:1129-1136
D'Hooghe 2019	D'Hooghe, T.,Fukaya, T.,Osuga, Y.,Besuyen, R.,Lopez, B.,Holtkamp, G. M.,Miyazaki, K.,Skillern, L.. Efficacy and safety of ASP1707 for endometriosis-associated pelvic pain: the phase II randomized controlled TERRA study. Human Reproduction. 2019. 34:813-823
Fu 2017	Fu, J.,Song, H.,Zhou, M.,Zhu, H.,Wang, Y.,Chen, H.,Huang, W.. Progesterone receptor modulators for endometriosis. Cochrane Database of Systematic Reviews. 2017. 7:CD009881
Harada 2017	Harada, T.,Kosaka, S.,Elliesen, J.,Yasuda, M.,Ito, M.,Momoeda, M.. Ethinylestradiol 20 mug/drospirenone 3 mg in a flexible extended regimen for the management of endometriosis-associated pelvic pain: a randomized controlled trial. Fertility & Sterility. 2017. 108:798-805
Jensen 2018	Jensen, J. T.,Schlaff, W.,Gordon, K.. Use of combined hormonal contraceptives for the treatment of endometriosis-related pain: a systematic review of the evidence. Fertility & Sterility. 2018. 110:137-152.e1
Lang 2018	Lang, J.,Yu, Q.,Zhang, S.,Li, H.,Gude, K.,von Ludwig, C.,Ren, X.,Dong, L.. Dienogest for Treatment of Endometriosis in Chinese Women: A Placebo-Controlled, Randomized, Double-Blind Phase 3 Study. Journal of Women's Health. 2018. 27:148-155
Osuga 2017	Osuga, Y., Fujimoto-Okabe, H., Hagino, A. Evaluation of the efficacy and safety of dienogest in the treatment of painful symptoms in patients with adenomyosis: a randomized, double-blind, multicenter, placebo-controlled study. Fertility & Sterility. 2017. 108:673-678.
Pontis 2017	Pontis, A., Nappi, L., Sorrentino, F., Paoletti, A.M., Melis, G. B., Angiono, S. Research development of a new GnRH antagonist (Elagolix) for the treatment of endometriosis: a review of the literature. Arch Gynecol Obstet. 2017. 295:827-832
Pontis 2016	Pontis, A.,D'Alterio, M. N.,Pirarba, S.,de Angelis, C.,Tinelli, R.,Angioni, S. Adenomyosis: a systematic review of medical treatment. Gynecological Endocrinology. 2016. 32:696-700
Shaaban 2015	Shaaban, O. M.,Ali, M. K.,Sabra, A. M.,Abd El Aal, D. E.. Levonorgestrel-releasing intrauterine system versus a low-dose combined oral contraceptive for treatment of adenomyotic uteri: a randomized clinical trial. Contraception. 2015. 92:301-7
Taylor 2017	Taylor, H. S.,Giudice, L. C.,Lessey, B. A.,Abrao, M. S.,Kotarski, J.,Archer, D. F.,Diamond, M. P.,Surrey, E.,Johnson, N. P.,Watts, N. B.,Gallagher, J. C.,Simon, J. A.,Carr, B. R.,Dmowski, W. P.,Leyland, N.,Rowan, J. P.,Duan, W. R.,Ng, J.,Schwefel, B.,Thomas, J. W.,Jain, R. I.,Chwalisz, K.. Treatment of Endometriosis-Associated Pain with Elagolix, an Oral GnRH Antagonist. New England Journal of Medicine. 2017. 377:28-40

Q8 – Alternatives to pharmacological and surgical management

Table App 57 Citations of included studies - alternatives to pharmacological and surgical management

Study ID	Citation
Almassinokiani 2016	Almassinokiani, Fariba,Khodaverdi, Sepideh,Solaymani-Dodaran, Masoud,Akbari, Peyman,Pazouki, Abdolreza. Effects of Vitamin D on Endometriosis-Related Pain: A Double-Blind Clinical Trial. Medical science monitor : international medical journal of experimental and clinical research. 2016. 22:4960

Study ID	Citation
Chong 2018	Chong, Ooi Thye,Critchley, Hilary Od,Williams, Linda J.,Haraldsdottir, Erna,Horne, Andrew W.,Fallon, Marie. The impact of meridian balance method electro-acupuncture treatment on chronic pelvic pain in women: a three-armed randomised controlled feasibility study using a mixed-methods approach. British Journal of Pain. 2018. 12:238-249
Cobellis 2011	Cobellis, Luigi,Castaldi, Maria Antonietta,Giordano, Valentino,Trabucco, Elisabetta,De Franciscis, Pasquale,Torella, Marco,Colacurci, Nicola. Effectiveness of the association micronized N-Palmitoylethanolamine (PEA)–transpolydatin in the treatment of chronic pelvic pain related to endometriosis after laparoscopic assessment: a pilot study. European Journal of Obstetrics and Gynecology. 2011. 158:82-86
Evans 2019	Evans, S.,Fernandez, S.,Olive, L.,Payne, L. A.,Mikocka-Walus, A.. Psychological and mind-body interventions for endometriosis: A systematic review. Journal of Psychosomatic Research. 2019. 124:109756
Goncalves 2017	Goncalves, A. V.,Barros, N. F.,Bahamondes, L.. The Practice of Hatha Yoga for the Treatment of Pain Associated with Endometriosis. Journal of Alternative and Complementary Medicine. 2017. 23:45-52
Indraccolo 2017	Indraccolo, U.,Indraccolo, S. R.,Mignini, F.. Micronized palmitoylethanolamide/trans-polydatin treatment of endometriosis-related pain: a meta-analysis. Annali Dell'Istituto Superiore di Sanita. 2017. 53:125-134
O'Hara 2019	O'Hara, R.,Rowe, H.,Fisher, J.. Self-management in condition-specific health: A systematic review of the evidence among women diagnosed with endometriosis. BMC Women's Health. 2019. 19:80
Santanam 2013	Santanam, Nalini,Kavtaradze, Nino,Murphy, Ana,Dominguez, Celia,Parthasarathy, Sampath. Antioxidant supplementation reduces endometriosis-related pelvic pain in humans. Translational Research. 2013. 161:189-195
Schwertner 2013	Schwertner, C. André,Conceição Dos Santos, Dalferth Claudia,Costa, Cristina Custodio Gislene,Deitos, L. S. Alícia,De Souza, Sabino L. Andressa,De Souza, Sabino L. Izabel,Torres, Sabino L. Iraci,Da Cunha Filho, Sabino L. João,Caumo, Sabino L. Wolnei. Efficacy of melatonin in the treatment of endometriosis: A phase II, randomized, double-blind, placebo-controlled trial. Pain. 2013. 154:874-881
Teixeira 2017	Teixeira, M. Z.,Podgaec, S.,Baracat, E. C.. Potentized estrogen in homeopathic treatment of endometriosis-associated pelvic pain: A 24-week, randomized, double-blind, placebo-controlled study. European Journal of Obstetrics and Gynecology and Reproductive Biology. 2017. 211:48-55
Van Niekerk 2019	Van Niekerk, L.,Weaver-Pirie, B.,Matthewson, M.. Psychological interventions for endometriosis-related symptoms: a systematic review with narrative data synthesis. Archives of Women's Mental Health. 2019. 22:723-735
Xu 2017	Xu, Y.,Zhao, W.,Li, T.,Zhao, Y.,Bu, H.,Song, S.. Effects of acupuncture for the treatment of endometriosis-related pain: A systematic review and meta-analysis. PLoS ONE. 2017. 12(10):e0186616
Zarbo 2018	Zarbo, C.,Brugnera, A.,Frigerio, L.,Malandrino, C.,Rabboni, M.,Bondi, E.,Compare, A.. Behavioral, cognitive, and emotional coping strategies of women with endometriosis: a critical narrative review. Archives of Women's Mental Health. 2018. 21:1-13

Q9a – Surgical management

Table App 58 Citations of included studies - surgical management

Study ID	Citation
Arcoverde 2019	Arcoverde, F. V. L.,Andres, M. D. P.,Borrelli, G. M.,Barbosa, P. D. A.,Abrao, M. S.,Kho, R. M.. Surgery for Endometriosis Improves Major Domains of Quality of Life: A Systematic Review and Meta-Analysis. Journal of Minimally Invasive Gynecology. 2019. 26:266-278
Arendas 2015	Arendas, K.,Foster, W. G.,Leyland, N. A.. Impact of surgical excision of deep infiltrating bowel endometriosis on health-related quality of life: Review of current literature. Journal of Endometriosis and Pelvic Pain Disorders. 2015. 7:3-9
Balla 2018	Balla, A.,Quaresima, S.,Subiela, J. D.,Shalaby, M.,Petrella, G.,Sileri, P.. Outcomes after rectosigmoid resection for endometriosis: a systematic literature review. International Journal of Colorectal Disease. 2018. 33:835-847
Barra 2018	Barra, F.,Scala, C.,Biscaldi, E.,Vellone, V. G.,Ceccaroni, M.,Terrone, C.,Ferrero, S.. Ureteral endometriosis: A systematic review of epidemiology, pathogenesis, diagnosis, treatment, risk of malignant transformation and fertility. Human Reproduction Update. 2018. 24:710-730
Brown 2014	Brown, J.,Farquhar, C.. Endometriosis: An overview of Cochrane Reviews. Cochrane Database of Systematic Reviews 2014, Issue 3. Art. No.: CD009590
Cavaco-Gomes 2017	Cavaco-Gomes, J.,Martinho, M.,Gilabert-Aguilar, J.,Gilabert-Estelles, J.. Laparoscopic management of ureteral endometriosis: A systematic review. European Journal of Obstetrics and Gynecology and Reproductive Biology. 2017. 210:94-101
Chaichian 2017	Chaichian, S.,Kabir, A.,Mehdizadehkashi, A.,Rahmani, K.,Moghimi, M.,Moazzami, B.. Comparing the efficacy of surgery and medical therapy for pain management in endometriosis: A systematic review and meta-analysis. Pain Physician. 2017. 20:185-195
Chen 2019	Chen, Y.,Wang, H.,Wang, S.,Shi, X.,Wang, Q.,Ren, Q.. Efficacy of ten interventions for endometriosis: A network meta-analysis. Journal of Cellular Biochemistry. 2019. 120:13076-13084
Cranney 2017	Cranney, R.,Condous, G.,Reid, S.. An update on the diagnosis, surgical management, and fertility outcomes for women with endometrioma. Acta Obstetricia et Gynecologica Scandinavica. 2017. 96:633-643

Study ID	Citation
Daniilidis 2017	Daniilidis, A.,Chatzistamatiou, K.,Assimakopoulos, E.. Is there a role for single-port laparoscopy in the treatment of endometriosis?. Minerva Ginecologica. 2017. 69:488-503
De Paula Andres 2017	de Paula Andres, M.,Borrelli, G. M.,Kho, R. M.,Abrao, M. S.. The current management of deep endometriosis: a systematic review. Minerva Ginecologica. 2017. 69:587-596
Franck 2018	Franck, C.,Poulsen, M. H.,Karampas, G.,Giraldi, A.,Rudnicki, M.. Questionnaire-based evaluation of sexual life after laparoscopic surgery for endometriosis: a systematic review of prospective studies. Acta Obstetricia et Gynecologica Scandinavica. 2018. 97:1091-1104
Fritzer 2017	Fritzer, N.,Hudelist, G.. Love is a pain? Quality of sex life after surgical resection of endometriosis: a review. European Journal of Obstetrics and Gynecology and Reproductive Biology. 2017. 209:72-76
Garcia 2011	Garcia, L.,Isaacson, K.. Adenomyosis: Review of the Literature. Journal of Minimally Invasive Gynecology. 2011. 18:428-437
Grimbizis 2014	Grimbizis, G. F.,Mikos, T.,Tarlatzis, B.. Uterus-sparing operative treatment for adenomyosis. Fertility and Sterility. 2014. 101:472-487.e8
Meuleman 2011	Meuleman, C.,Tomassetti, C.,D'Hoore, A.,Van Cleynenbreugel, B.,Penninckx, F.,Vergote, I.,D'Hooghe, T.. Surgical treatment of deeply infiltrating endometriosis with colorectal involvement. Human Reproduction Update. 2011. 17:311-326
Palla 2017	Palla, V. V.,Karaolanis, G.,Katafigiotis, I.,Anastasiou, I.. Ureteral endometriosis: A systematic literature review. Indian Journal of Urology. 2017. 33:276-282
Pundir 2017	Pundir, J.,Omanwa, K.,Kovoor, E.,Pundir, V.,Lancaster, G.,Barton-Smith, P.. Laparoscopic Excision Versus Ablation for Endometriosis-associated Pain: An Updated Systematic Review and Meta-analysis. Journal of Minimally Invasive Gynecology. 2017. 24:747-756
Rehmer 2019	Rehmer, J. M.,Flyckt, R. L.,Goodman, L. R.,Falcone, T.. Management of Endometriomas. Obstetrical and Gynecological Survey. 2019. 74:232-240
Riley 2019	Riley, K. A.,Benton, A. S.,Deimling, T. A.,Kunselman, A. R.,Harkins, G. J.. Surgical Excision Versus Ablation for Superficial Endometriosis-Associated Pain: A Randomized Controlled Trial. Journal of Minimally Invasive Gynecology. 2019. 26:71-77
Rindos 2017	Rindos, N. B.,Mansuria, S.. Diagnosis and management of abdominal wall endometriosis: A systematic review and clinical recommendations. Obstetrical and Gynecological Survey. 2017. 72:116-122
Vercellini 2014	Vercellini, P.,Consonni, D.,Barbara, G.,Buggio, L.,Frattaruolo, M. P.,Somigliana, E.. Adenomyosis and reproductive performance after surgery for rectovaginal and colorectal endometriosis: A systematic review and meta-analysis. Reproductive BioMedicine Online. 2014. 28:704-713
Younes 2018	Younes, G.,Tulandi, T.. Conservative Surgery for Adenomyosis and Results: A Systematic Review. Journal of Minimally Invasive Gynecology. 2018. 25:265-276

Q9b – Combination of surgery and hormonal treatment

Table App 59 Citations of included studies - combination of surgery and hormonal treatment

Study ID	Citation
Chen 2017	Chen, Y.J., Hsu, T.F., Huang, B.S., Tsai, H.W., Chang, Y.H., Wang, P.H. Postoperative maintenance levonorgestrel-releasing intrauterine system and endometrioma recurrence: a randomized controlled study. American Journal of Obstetrics & Gynecology. 2017. 216:582.e1-9.
Huang 2018	Huang, C., Wu, M., Liu, Z., Shi, H., Han, Y., Song, X. Clinical efficacy and safety of gonadotropin-releasing hormone agonist combined with laparoscopic surgery in the treatment of endometriosis. International Journal of Clinical and Experimental Medicine. 2018. 11:4132-4137.
Song 2018	Song, S.Y., Park, M., Lee, G.W., Lee, K.H., Chang, H.K., Kwak, S.M., Yoo, H.J. Efficacy of levonorgestrel releasing intrauterine system as a postoperative maintenance therapy of endometriosis: A meta-analysis. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2018. 231:85-92
Tanmahasamut 2017	Tanmahasamut, P., Saejong, R., Rattanachaiyanont, M., Angsuwathana, S., Techatraisak, K., Sanga-Areekul, N. Postoperative desogestrel for pelvic endometriosis-related pain: a randomized controlled trial. Gynecological Endocrinology. 2017. 33:534-539.

Q9c – Hysterectomy

Table App 60 Citations of included studies - hysterectomy

Study ID	Citation
Ferrero 2010	Ferrero, S.,Remorgida, V.,Venturini, P. L.. Endometriosis. BMJ clinical evidence. 2010. 08:802
Hickey 2010	Hickey, M.,Ambekar, M.,Hammond, I.. Should the ovaries be removed or retained at the time of hysterectomy for benign disease?. Human Reproduction Update. 2010. 16(2):131-141
Michalapoulos 2012	Michalopoulos, G.,Makris, V.,Daniilidis, A.,Sardeli, C.,Dinas, K.,Giannoulis, C.,Loufopoulos, P. D.. Surgical treatment of endometriosis. Current Women's Health Reviews. 2012. 8:131-137
Oliveira 2018	Oliveira, M. A. P.,Crispi, C. P.,Brollo, L. C.,De Wilde, R. L.. Surgery in adenomyosis. Archives of Gynecology and Obstetrics. 2018. 297:581-589
Tan 2013	Tan, B. K.,Maillou, K.,Mathur, R. S.,Prentice, A.. A retrospective review of patient-reported outcomes on the impact on quality of life in patients undergoing total abdominal hysterectomy and bilateral salpingo-oophorectomy for endometriosis. European Journal of Obstetrics and Gynecology and Reproductive Biology. 2013. 170:533-538

Q10 – Management strategies to enhance fertility

No new relevant studies were identified in the literature search.

Q11 – Follow-up

No new relevant studies were identified in the literature search.

Q12 – Secondary prevention

Table App 61 Citations of included studies - secondary prevention

Study ID	Citation
Chen 2017	Chen YJ, Hsu TF, Huang BS, Tsai HW, Chang YH, Wang PH. Postoperative maintenance levonorgestrel-releasing intrauterine system and endometrioma recurrence: a randomized controlled study. American Journal of Obstetrics & Gynecology. 2017. 216:582.e1-9.
Huang 2018	Huang C, Wu M, Liu Z, Shi H, Han Y, Song X. Clinical efficacy and safety of gonadotropin-releasing hormone agonist combined with laparoscopic surgery in the treatment of endometriosis. International Journal of Clinical and Experimental Medicine. 2018. 11:4132-4137