

Topic Brief: Diagnosis and Treatment for Endometriosis

Date: 09/27/022

Nomination Number: 0985

Purpose: This document summarizes the information addressing a nomination submitted by a non-profit organization on May 15, 2022, through the Effective Health Care Website. This information was used to inform the Evidence-based Practice Center (EPC) Program decisions about whether to produce an evidence report on the topic, and if so, what type of evidence report would be most suitable.

Issue: Endometriosis is a chronic debilitating condition that affects many women. However, diagnosis is difficult, with many years delay from symptoms to diagnosis. Despite an astounding number of recent systematic reviews, the level of evidence still remains low for most questions of diagnosis and treatment. For these reasons, endometriosis is of great interest to patient, clinicians, guideline groups and research funders.

Findings: The scope of this topic met all EHC Program selection criteria and was considered for a systematic review and an evidence map. However, it was not selected.

Background

- Endometriosis is a chronic gynecologic disorder whose principal adverse effects are chronic pain and infertility. The exact prevalence of endometriosis is unknown, but estimates range from 2 to 10% within the general female population but up to 50% in infertile women ^{1,2} The clinical symptoms or signs of endometriosis are variable and unpredictable in both presentation and course. Dysmenorrhea, chronic pelvic pain, dyspareunia, uterosacral ligament nodularity, and an adnexal mass (either symptomatic or asymptomatic) are among the common manifestations. A significant number of women with endometriosis remain asymptomatic. Endometriosis impacts relationships and quality of life. Healthcare costs are comparable to other common diseases such as type 2 diabetes, rheumatoid arthritis, and Crohn's disease. ³
- Despite all of this, there still exists an average lag of 4-7 years between the onset of symptoms and a reliable diagnosis. ^{4,5} The "gold standard" for diagnosis has been laparoscopic detection of lesions with biopsy and histologic confirmation. But because of the low sensitivity / specificity of non-invasive exams, the higher risks of surgery, and possibility of false-negative biopsy results, no clinical guideline group has recommended diagnostic laparoscopy as the first step in the diagnostic pathway. ^{6,7}
- Treatment options aim to reduce symptoms and improve fertility by pharmacologic, surgical, or psycho-social approaches. These include hormone suppression, pro-apoptotic and anti-inflammatory drugs that target on endometriotic tissue, surgical removal or

destruction of endometriotic lesions, and alternative approaches such as diet, yoga or behavioral therapy.

- Two ACOG guideline documents have not been updated in several years.^{6,8}

Nomination Summary and Stakeholder Engagement

- The nomination was submitted by representatives from two groups, one representing women and another representing adolescents. They noted that ACOG guidelines on the topic are several years old. A clinical specialty group and research funder also expressed interest in this topic.
- After the preliminary search of the literature and discussion with interested groups, the scope was narrowed to focus on surgical treatment modalities would benefit guideline groups and patients.

Scope 1 (Evidence Map)

1. What approaches for diagnosing endometriosis have been studied that report on effectiveness, comparative effectiveness, and harms?
 - a. What are the characteristics of patients studied (e.g., presenting symptoms, age)?
 - b. What comparisons have been studied?
 - c. What outcomes have been studied?
 - d. What are the reported outcomes, and do they vary by patient characteristics?
2. What of treatments for endometriosis have been studied that report on effectiveness, comparative effectiveness, and harms?
 - a. What are the characteristics of patients studied (e.g., presenting symptoms, age)?
 - b. What comparisons have been studied?
 - c. What outcomes have been studied?
 - d. What are the reported outcomes, and do they vary by patient characteristics?
3. What are gaps in the current research and what specific research is needed to fill these gaps?

Table 1. Evidence Map Questions and PICOTS (population, intervention, comparator, outcome, timing and setting)

	Key Question 1: Diagnosis	Key Question 2: Treatment
Population	Individuals ages 14-54 with symptoms of endometriosis Subgroups: age, presenting symptoms (e.g., subtypes of endometriosis), duration of symptoms, gender identity (e.g., cis/trans/non-binary), racial/ethnic identities, socioeconomic status, insurance status, geography (e.g., rural vs. urban; region of the U.S.), other health equity considerations	Individuals ages 14-54 with endometriosis Subgroups: age, presenting symptoms (e.g., subtypes of endometriosis), desired fertility outcomes (i.e., immediate vs future vs no fertility improvement) duration of symptoms, gender identity (e.g., cis/trans/non-binary), racial/ethnic identities, socioeconomic status, insurance status, geography (e.g., rural vs. urban; region of the U.S.), other health equity considerations
Intervention	Diagnostic imaging techniques, symptom questionnaires, physical examination, biomarkers, visualization only during diagnostic laparoscopy, combination of methods	<ol style="list-style-type: none"> 1. Surgical interventions (e.g., excision, ablation, cauterization, drainage) 2. Pharmacological interventions (i.e., medical pain management)

		3. Non-surgical/medical interventions (e.g., therapy-based interventions (Cognitive-Behavioral Therapy), yoga, diet, dietary supplements, medical cannabis, acupuncture)
Comparator	Diagnostic laparoscopy with histologic diagnosis, Other diagnostic approach	Other Surgical intervention; non-surgical/medical intervention; pharmacological interventions, placebo/usual care
Outcomes	Sensitivity/specificity, time from initiation of diagnostic procedures to initiation of treatment/management interventions Harms of diagnostic laparoscopy	Pain, quality of life, fertility (e.g., ovarian functioning, pregnancy rate), menstrual cycle (e.g., dysmenorrhea, heavy menstrual bleeding), sexual functioning, disease/pain recurrence, time to disease/pain recurrence, reoperation rate, extra-pelvic symptoms (symptoms of deeply infiltrating endometriosis (e.g., deep dyspareunia; bladder pain; low back pain; urinary frequency/urgency, blood in the urine; bowel frequency/urgency, incomplete emptying, constipation, and blood in the stool), harms

Scope 2: Systematic review of surgical interventions

1. What are the effectiveness, comparative effectiveness, and harms of surgical approaches for treating endometriosis?
 - a. How do outcomes vary by disease stage and other patient characteristics?
 - b. How do outcomes vary by intervention characteristics?

Table 2. SR Questions and PICOTS (population, intervention, comparator, and outcome)

	Key Question : Treatment
Population	Individuals ages 14-54 with endometriosis Subgroups: stage of endometriosis, age, symptoms, desired fertility (i.e., immediate vs future vs no fertility) duration of symptoms, gender identity (e.g., cis/trans/non-binary), racial/ethnic identities, socioeconomic status, insurance status, geography (e.g., rural vs. urban; region of the U.S.), other health equity considerations
Intervention	1. Surgical interventions (e.g., excision, ablation, cauterization, drainage) Subgroups: specific procedure, open vs laparoscopic, robotic vs. laparoscopic
Comparator	1. Placebo/usual care 2. Other surgical intervention 3. Pharmacological interventions (i.e., medical pain management) 4. Non-surgical/medical interventions (e.g., therapy-based interventions (Cognitive-Behavioral Therapy), yoga, diet, dietary supplements, medical cannabis, acupuncture)
Outcomes	Pain, quality of life, fertility (e.g., ovarian functioning, pregnancy rate), menstrual cycle (e.g., dysmenorrhea, heavy menstrual bleeding), sexual functioning or satisfaction, disease/pain recurrence, time to disease/pain recurrence, reoperation rate, extra-pelvic symptoms, symptoms of deeply infiltrating endometriosis (e.g., deep dyspareunia; bladder symptoms; low back pain; bowel symptoms), harms

Assessment Methods

See Appendix A.

Summary of Literature Findings

- **One: Evidence map:**
 - We found 32 systematic reviews that cover much of the scope on diagnosis, and 58 which cover many parts of the scope on treatment. These reviews vary by inclusion criteria and rigor and include many of the same research studies with varying conclusions. The primary literature continues to grow, with additional primary studies that need to be incorporated.
 - The literature (and research gaps) may be difficult to synthesize because of the heterogeneity of disease stages, diagnostic and treatment approaches and outcomes for the broad topic of endometriosis as initially proposed.
- **Two: Systematic review on surgical approaches:**
 - While we found 13 recent systematic reviews on surgical interventions, the information is fragmented, and new primary studies were identified. A new high-quality systematic review focusing on surgical interventions (revised PICOTs) would be useful for patient advocates and guideline developers to promote practice change. A network meta-analysis approach might address the paucity of head-to-head comparisons. A “best evidence” approach (for example, including well designed non-RCTs) might help identify less common harms and outcomes and help guide decision-making. The topic might benefit from modeling outcomes that might be useful in a shared decision-making applications (such as Wisercare©)

Details on existing literature for Scope1: Evidence map

KQ1: Diagnosis

A recent (2022) CPG commissioned by the European Society for Human Reproduction and Embryology (ESHRE) was supported by systematic review. Unfortunately, the review was not published independently, and its usefulness to a US audience is in question.⁷ The ESHRE CPG includes many low SOE conclusions, such as:

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

The group found insufficient evidence for the following points, which are listed as “Good Practice Pointers” based on expert opinion.

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

The group found even less evidence on the following points, which they mention as a Guideline Development Group (GDG) “statement.”

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

In addition to the CPG, we found 32 systematic reviews addressing KQ1 (see Table 2). Several addressed subtypes of endometriosis (i.e., deep endometriosis). However, none reported information on other subgroups of interest to the nominator (duration of symptoms, gender identity (e.g., cis/trans/non-binary), racial/ethnic identities, socioeconomic status, insurance status, geography (e.g., rural vs. urban; region of the U.S.), other health equity considerations.

We identified 13 studies relevant to KQ1. Most were on imaging during laparoscopy. Though we restricted to RCTs we identified three non-RCTs. The evidence base may be larger if non-RCTs are included.

Because of the heterogeneity of the literature, the low strength of evidence for approaches considered as “usual care,” and the growing field of non-invasive diagnostic methods, an evidence map on diagnostic considerations would be quite useful to research funders. One published protocol describes a scoping review of diagnostic pathways affecting diagnostic delay.⁹ When contacted, the author reports that the manuscript (full report) will be submitted for publication in September 2022. If this review is published before the scope of work for the evidence map is finalized, it might influence the PICOTS.

KQ2: Treatment

KQ2 has been covered in **58** recent systematic reviews, and a CPG. The majority of the SRs have few definitive findings because of limited evidence. The ESHRE CPG reviewed the evidence on a wide range of treatment approaches, and made 59 recommendations.⁷ Of these, there are only six with moderate SOE, 23 with low SOE, with 18 with very low SOE, and 13 listed as expert opinion/insufficient data to be graded.

The Moderate SOE recommendations are not very strongly worded, for example:

- It is recommended to **offer** women hormone treatment (combined hormonal contraceptives, progestogens, GnRH agonists or GnRH antagonists) as one of the options to reduce endometriosis-associated **pain**.
- It is recommended to **prescribe** women a levonorgestrel-releasing intrauterine system or an etonogestrel-releasing subdermal implant to reduce endometriosis-associated **pain**.
- Clinicians should **consider** prescribing combined hormonal add-back therapy alongside GnRH agonist therapy to prevent bone loss and hypoestrogenic symptoms.

We identified > 130 relevant RCTs and 84 active clinical trials. The large volume, the heterogeneity of disease types, interventions, and outcomes makes an evidence map especially useful.

Table 3. Literature identified for the Evidence Map Questions

Evidence Map:	Systematic reviews (6/2019-6/2022)	Primary studies (6/2017-6/2022)
Question 1 Diagnosing endometriosis	Total: 32 <ul style="list-style-type: none"> • Cochrane- 0 • AHRQ-0 • Other 32 Specific focus of SR:	Total: 13 <ul style="list-style-type: none"> • RCT (10) <ul style="list-style-type: none"> • Imaging during laparoscopy (6)⁴¹⁻⁴⁶

	<ul style="list-style-type: none"> • Biomarkers- (12)¹⁰⁻²¹ • Imaging alone (1)²² • Imaging during laparoscopy (3)²³⁻²⁵ • Deep endometriosis (15)²⁶⁻⁴⁰ • diagnostic pathway scoping review- (in progress, published protocol): (1)⁹ 	<ul style="list-style-type: none"> • Biomarkers: (3)⁴⁷⁻⁴⁹ • Imaging / AI (1)⁵⁰ • NRCT (3):⁵¹⁻⁵³ <p>Clinicaltrials.gov: 64</p>
Question 2: Treatment of endometriosis	<p>Total: 58 Cochrane- 4⁵⁴⁻⁵⁷</p> <ul style="list-style-type: none"> • AHRQ-0 • Other -54 <p>Focus of SR:</p> <ul style="list-style-type: none"> • Type of endometriosis: Deep (9)⁵⁸⁻⁶⁷; Endometrioma (9)⁶⁸⁻⁷⁶; Extrapelvic (10)⁷⁷⁻⁸⁶ Mild (1)⁸⁷ • Type of treatment: Surgical (8)^{54, 87-93} Medical (6)^{55, 94-98} Diet (2)^{99, 100} Exercise (2)^{101, 102} Behavioral (5)¹⁰³⁻¹⁰⁷ • Specific outcomes: Fertility (5)^{56, 88-90, 108} Obstetric (2)^{109, 110} Recurrence (6)^{55, 59, 97, 98, 111, 112} 	<p>Total:</p> <ul style="list-style-type: none"> • RCT (131) • Published 2021-2022: (49) <p>Clinicaltrials.gov: 82</p>

Two: Details on available evidence for scope 2: Systematic review of surgical interventions

We identified 14 systematic reviews, with 2 from Cochrane. The scope of these reviews were overlapping but none comprehensively covered the entire scope. Thus, current information is scattered across multiple sources. We identified 26 RCTs and 37 non-RCTs focused on surgical interventions.

Table 4: Literature identified for the systematic review question

Systematic Review	Systematic reviews (6/2019-6/2022)	Primary studies (6/2017-6/2022)
Question 2: Treatment of endometriosis	<p>Total: 14 Cochrane- 2^{54, 55}</p> <ul style="list-style-type: none"> • AHRQ-0 • Other -12^{60, 61, 65, 66, 76, 87, 89-93, 113} <p>Focus of SR:</p> <p>Stage:</p> <ul style="list-style-type: none"> • Deep endometriosis- 5^{60, 61, 65, 66, 93} • Endometrioma-1⁷⁶ • Mild-1⁸⁷ <p>Outcome:</p> <ul style="list-style-type: none"> • Fertility-2^{89, 90} <p>Approach:</p> <ul style="list-style-type: none"> • Laparoscopy- 3^{54, 91, 92} • Surgery +/1 adjunctive medical¹⁵⁵ 	<p>Total:</p> <ul style="list-style-type: none"> • RCT (26) • Cohort (37) <p>Clinicaltrials.gov: 31</p>

Table 5 summarizes the conclusions from the three recent SR on surgical treatment published in higher impact journals (impact factors > 4.0)

Table 5: Summary of Recent SR on Surgical treatment

Author, Year, journal	Number of RCTs (patients)	Intervention vs comparator	Conclusion	SOE
Bafort, 2020 ⁵⁴ Cochrane	14 (1563)	laparoscopic surgery vs. diagnostic laparoscopy only	increases viable intrauterine pregnancy rates confirmed by ultrasound	Moderate
		laparoscopic surgery vs. diagnostic laparoscopy only	Uncertain: Overall pain, quality of life, live birth rates, adverse effects	Very low-quality evidence.
Chen, 2020 ⁵⁵ Cochrane	16 (3457)	Pre-op hormonal suppression vs. surgery alone	Uncertain: Pain at 12 months; disease recurrence at 12 months pregnancy rates	Very low-quality evidence.
		Post-op hormonal suppression vs. surgery alone	Lower disease recurrence at 12 months	Low
		Post-op hormonal suppression vs. surgery alone	Pregnancy rate is probably increased	Moderate
		Post-op vs. pre- op hormonal suppression	Uncertain: Pain at 12 months; disease recurrence at 12 months; pregnancy rate	Very low-quality
Wattanaying-charoenchai, 2021 ⁷³ BJOG	6 RCTs (675) and 16 cohorts (3089)	Any hormonal post-op suppression vs none	NMA of RCTs: no evidence that hormonal treatment prevents postoperative endometrioma recurrence. cohort NMA: protective effect of OC and progestin regimens, especially long-term treatment	Not reported

See Appendix B for detailed assessments of all EPC selection criteria.

Summary of Selection Criteria Assessment

- This nomination meets all selection criteria for two new evidence review products.
One: evidence map: We found 32 systematic reviews that address diagnosis, and 58 systematic reviews which address treatment. We estimate 90-100 primary studies about diagnosis and treatment of endometriosis. The large volume, the heterogeneity of disease types, interventions, and outcomes makes an evidence map especially useful. SR authors have concluded that further research is needed on live birth rates, adverse events, different subtypes of endometriosis, and comparing laparoscopic interventions with lifestyle and medical interventions. However, these broad recommendations could be honed with a high-quality evidence map. The map could be used to guide research funders, study designs and outcome harmonization that would close many evidence gaps in both diagnosis and treatment of endometriosis

Two: Systematic review of surgical treatment:

We found 14 systematic reviews that address surgical treatment of endometriosis. We did not consider these systematic reviews duplicative because findings are scattered across several sources are less useful to guideline developers. We estimate ~ 20-50 new primary studies about

surgical treatment of endometriosis. A new high-quality systematic review focusing on surgical interventions would be useful for patient advocates and guideline developers to promote practice change. An updated review would be highly impactful and valuable and could inform clinical guidance, patient education, and enhanced decision-making

Please see Appendix B for detailed assessments of individual EPC Program selection criteria.

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Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Acknowledgements

Emily Gean

Robin Paynter

Christine Chang

This report was developed by staff at the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD. The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. No statement in this article should be construed as an official position of the Agency for Healthcare Research and Quality or of the U.S. Department of Health and Human Services.

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Appendix A: Methods

We assessed nomination for priority for a systematic review or other AHRQ Effective Health Care report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix B for detailed description of the criteria.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Absence of Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last Three years 6/28/2019 through 6/27/2022 on nomination questions from these sources:

- AHRQ: Evidence reports and technology assessments
 - AHRQ Evidence Reports <https://www.ahrq.gov/research/findings/evidence-based-reports/index.html>
 - EHC Program <https://effectivehealthcare.ahrq.gov/>
 - AHRQ Technology Assessment Program <https://www.ahrq.gov/research/findings/ta/index.html>
- Cochrane Systematic Reviews <https://www.cochranelibrary.com/>
- PROSPERO Database (international prospective register of systematic reviews and protocols) <http://www.crd.york.ac.uk/prospéro/>
- PubMed <https://www.ncbi.nlm.nih.gov/pubmed/>
- Epistemonikos <https://www.epistemonikos.org/>

Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review

Librarians conducted a literature search in OVID/MEDLINE, Cochrane Central Register of Controlled Trials (CCRCT), Epistemonikos, ClinicalTrials.gov from the last five years 6/28/2017 through 6/27/2022 on the entire nomination scope. The same search was used to inform assessment for the proposed evidence map and systematic review.

Of an initial yield of 2231 articles, the librarians reviewed titles and sorted these into groups by key question and study design.

For the evidence map:

The author reviewed all titles and abstracts of systematic reviews identified in the search. The author reviewed abstracts restricted to RCT and diagnosis or treatment.

For the SR:

The author reviewed the titles and abstracts for each of the SRs and primary studies regardless of study type for the terms: surgical, laparoscopic, excision, or robotic.

Search strategy

Ovid MEDLINE(R) ALL <1946 to June 27, 2022>

Date searched: June 28, 2022

1 Endometriosis/ (24384)

2 endometriosis\$.ti,kf. (19993)

3 or/1-2 (27025)

4 exp Diagnostic Imaging/ or Magnetic Resonance Imaging/di, du or exp Ultrasonography/di, du or (di or du or us).fs. (5092495)

5 (diagnos* adj7 (imaging or MRI or "magnetic resonance" or sonograph* or transrectal* or transvaginal* or TVS or ultrasonograph* or ultrasound)).ti,ab,kf. (157641)

6 exp Biomarkers/ or biomarker\$.ti,kf. or (exp Laparoscopy/ and diagnos*.ti,kf.) or (laparoscop* adj5 diagnos*).ti,kf. or Physical Examination/ or (physical adj2 exam*).ti,kf. or (symptom\$.ti,kf. adj2 questionnaire*).ti,ab,kf. (957762)

7 or/4-6 (5823037)

8 and/3,7 (8652)

9 limit 8 to english language (7163)

10 9 not (Animals/ not Humans/) (7034)

11 limit 10 to yr="2019 -Current" (1317)

12 (meta-analysis or "systematic review").pt. or (meta-anal* or metaanal* or ((evidence or scoping or systematic or umbrella) adj3 (synthesis or review))).ti. (357007)

13 and/11-12 (69)

14 limit 10 to yr="2017 -Current" (1874)

15 (controlled clinical trial or randomized controlled trial).pt. or (trial or control or controlled or random*).ti,kf. (1332839)

16 and/14-15 (60)

17 observational study.pt. or exp cohort studies/ or (cohort or follow-up* or longitudinal or observational or prospective or retrospective).ti. (2549308)

18 and/14,17 (501)

19 Drainage/ or Endometrial Ablation Techniques/ or Laparoscopy/ or (ablat* or cauteriz* or cauteris* or drain* or excis* or laparoscop* or resect* or surgery or surgical).ti,ab,kf. (2590930)

20 exp Analgesia/ or Cannabis/ or Cannabidiol/ or "Medical Marijuana"/ or (analges* or cannabis or cannabidiol or CBD or "medical marijuana" or (pain adj2 (control* or manag*))).ti,ab,kf. (237101)

21 Acupuncture/ or Cognitive Behavioral Therapy/ or exp Diet/ or exp Dietary Supplements/ or Yoga/ or (nonpharmacological or non-pharmacological or nonsurgical or non-surgical or acupuncture or diet or dietary or supplement\$.ti,ab,kf. (892586)

22 or/19-21 (3603535)

23 and/3,22 (10676)

24 limit 23 to english language (9285)

25 24 not (Animals/ not Humans/) (9056)

26 limit 25 to yr="2019 -Current" (1991)

27 (meta-analysis or "systematic review").pt. or (meta-anal* or metaanal* or ((evidence or scoping or systematic or umbrella) adj3 (synthesis or review))).ti. (357007)

28 and/26-27 (117)

29 limit 25 to yr="2017 -Current" (2800)

30 (controlled clinical trial or randomized controlled trial).pt. or (trial or control or controlled or random*).ti,kf. (1332839)

31 and/29-30 (156)

32 observational study.pt. or exp cohort studies/ or (cohort or follow-up* or longitudinal or observational or prospective or retrospective).ti. (2549308)

33 and/29,32 (838)

Ovid EBM Reviews - Cochrane Central Register of Controlled Trials

Date searched: June 28, 2022

1. Endometriosis/ (923)
- 2 endometriosis\$.ti,kf. (1688)
- 3 or/1-2 (1930)
- 4 exp Diagnostic Imaging/ or Magnetic Resonance Imaging/di, du or exp Ultrasonography/di, du or (di or du or us).fs. (102506)
- 5 (diagnos* adj7 (imaging or MRI or "magnetic resonance" or sonograph* or transrectal* or transvaginal* or TVS or ultrasonograph* or ultrasound)).ti,ab,kf. (6038)
- 6 exp Biomarkers/ or biomarker\$.ti,kf. or (exp Laparoscopy/ and diagnos*.ti,kf.) or (laparoscop* adj5 diagnos*).ti,kf. or Physical Examination/ or (physical adj2 exam*).ti,kf. or (symptom\$.ti,kf. adj2 questionnaire*).ti,ab,kf. (32833)
- 7 or/4-6 (133581)
- 8 and/3,7 (196)
- 9 limit 8 to english language (181)
- 10 limit 9 to yr="2017 -Current" (56)
- 11 Drainage/ or Endometrial Ablation Techniques/ or Laparoscopy/ or (ablat* or cauteriz* or cauteris* or drain* or excis* or laparoscop* or resect* or surgery or surgical).ti,ab,kf. (253747)
- 12 exp Analgesia/ or Cannabis/ or Cannabidiol/ or "Medical Marijuana"/ or (analges* or cannabis or cannabidiol or CBD or "medical marijuana" or (pain adj2 (control* or manag*))).ti,ab,kf. (73503)
- 13 Acupuncture/ or Cognitive Behavioral Therapy/ or exp Diet/ or exp Dietary Supplements/ or Yoga/ or (nonpharmacological or non-pharmacological or nonsurgical or non-surgical or acupuncture or diet or dietary or supplement\$.ti,ab,kf. (137943)
- 14 or/11-13 (419789)
- 15 and/3,14 (1085)
- 16 limit 15 to english language (914)
- 17 limit 16 to yr="2017 -Current" (309)

Epistemonikos KQ1

Date searched: June 29, 2022

(title:(title:(endometriosis) AND title:(diagnos* OR imaging OR MRI OR "magnetic resonance" OR sonograph* OR transrectal* OR transvaginal* OR TVS OR ultrasonograph* OR ultrasound OR biomarker* OR exam OR examination OR questionnaire*)) OR abstract:(title:(endometriosis) AND title:(diagnos* OR imaging OR MRI OR "magnetic resonance" OR sonograph* OR transrectal* OR transvaginal* OR TVS OR ultrasonograph* OR ultrasound OR biomarker* OR exam OR examination OR questionnaire*))) (41)

Epistemonikos KQ2

Date searched: June 29, 2022

(title:(endometriosis) OR abstract:(endometriosis)) AND title:(ablat* OR cauteriz* OR cauteris* OR drain* OR excis* OR laparoscop* OR resect* OR surgery OR surgical OR analges* OR cannabis OR cannabidiol OR CBD OR "medical marijuana" OR pain nonpharmacological OR non-pharmacological OR nonsurgical OR non-surgical OR acupuncture OR diet OR dietary OR supplement* OR yoga) (77)

ClinicalTrials.gov KQ1

Date searched: June 29, 2022

AREA[OverallStatus] EXPAND[Term] COVER[FullMatch] ("Recruiting" OR "Not yet recruiting" OR "Active, not recruiting" OR "Enrolling by invitation") AND AREA[ConditionSearch] Endometriosis AND AREA[InterventionSearch] (diagnosis OR imaging OR MRI OR EXPAND[Concept] "magnetic resonance" OR sonographic OR transrectal OR transvaginal OR TVS OR ultrasonographic OR ultrasound OR biomarker OR exam OR examination OR questionnaire) AND AREA[Gender] EXPAND[Term] COVER[FullMatch] NOT "Male" AND AREA[StdAge] EXPAND[Term] COVER[FullMatch] "Adult" AND AREA[StudyFirstPostDate] EXPAND[Term] RANGE[06/29/2019, 06/29/2022] (64)

ClinicalTrials.gov KQ2

Date searched: June 29, 2022

AREA[OverallStatus] EXPAND[Term] COVER[FullMatch] ("Recruiting" OR "Not yet recruiting" OR "Active, not recruiting" OR "Enrolling by invitation") AND AREA[ConditionSearch] Endometriosis AND AREA[InterventionSearch] (ablation OR cauterization OR cauterisation OR drainage OR excision OR laparoscopic OR resection OR surgery OR surgical OR analgesic OR cannabis OR cannabidiol OR CBD OR "medical marijuana" OR pain OR nonpharmacological OR non-pharmacological OR nonsurgical OR non-surgical OR acupuncture OR diet OR dietary OR supplement OR yoga) AND AREA[Gender] EXPAND[Term] COVER[FullMatch] NOT "Male" AND AREA[StdAge] EXPAND[Term] COVER[FullMatch] "Adult" AND AREA[StudyFirstPostDate] EXPAND[Term] RANGE[06/29/2019, 06/29/2022] (82)

Value

We assessed the nomination for value. We considered whether or not the clinical, consumer, or policymaking context had the potential to respond with evidence-based change; and if a partner organization would use this evidence review to influence practice.

Appendix B. Selection Criteria Assessment

Selection Criteria	Assessment
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes
1b. Is the nomination a request for an evidence report?	Yes
1c. Is the focus on effectiveness or comparative effectiveness?	Yes
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	Endometriosis is a disease characterized by the presence of endometrial tissue outside the uterus, usually associated with pain, infertility and other symptoms. The exact prevalence of endometriosis is unknown, but estimates range from 2% to 10% within the general female population and up to 50% in infertile women.
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes. Endometriosis is requires long term treatment and is costly for both diagnosis and treatment.
2c. Incorporates issues around both clinical benefits and potential clinical harms	Yes. The gold standard for diagnosis is diagnostic laparoscopy with tissue biopsy, which is costly, invasive and incurs risks of surgery and anesthesia. There is no evidence that immediate laparoscopy yields improved outcomes compared to empiric therapy. ⁵⁴ Much of the clinical guidance is based on low quality evidence and expert opinion.
2d. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes.
3. Desirability of a New Evidence Review/Absence of Duplication	
3. A recent high-quality systematic review or other evidence review is not available on this topic	1. Evidence Map: There are 23 recent reviews on KQ1 (diagnosis), and one in-progress scoping review on timing and delays to diagnosis is soon to be published (author communication). We identified 58 systematic reviews on

	<p>treatment, four of them by the Cochrane Collaboration. They addressed many of the treatments of interest. However, to our knowledge, an overall summary of the research gaps has not been developed. An evidence map would help research funders plan future studies appropriately.</p> <p>2. Systematic Review: We found 14 existing SR on surgical treatment for endometriosis. However, the comparative effectiveness and harms have not been summarized by disease stage in a way to inform clinical guidelines.</p>
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	The current standard of care is unclear, as it is largely based on low quality evidence. A recent comparison of 8 treatment guidelines found only one area of concordance (use of a combined oral contraceptive pill or progestogens are recommended for endometriosis associated pain) but wide discrepancies on other treatment approaches and outcomes. ¹¹⁴
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	With outdated and low-evidence guidance from sources in the USA (such as ACOG), we did not attempt to search for practice variation
5. Primary Research	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	<p>The primary literature base continues to grow, with 13 new primary studies on diagnosis in the last 2 years.</p> <p>Based on our preliminary search, the evidence map is likely to be large (> 100 studies). The systematic review is likely to be medium (36-90 studies)</p>
6. Value	
6a. The proposed topic exists within a clinical, consumer, or policy-making context that is amenable to evidence-based change	Yes.
6b. Identified partner who will use the systematic review to influence practice (such as a guideline or recommendation)	Yes. Patient groups, clinical groups, and a research funder have expressed interest.

Abbreviations: AHRQ=Agency for Healthcare Research and Quality;