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Diagnosis and management of endometriosis: a systematic review of international and national guidelines

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Running title: A systematic review of endometriosis guidelines.

Abstract

Background

The development of robust clinical guidelines requires standardised development methods informed by robust evidence synthesis.

Objectives

We evaluated the methodological quality of endometriosis guidelines, mapped their recommendations, and explored the relationships between recommendations and research evidence.

Search Strategy

We searched: [1] EMBASE; [2] Medline; and [3] Pubmed from inception to February 2016.

Selection Criteria

We included guidelines related to the diagnosis and management of endometriosis.

Data Collection and Analysis

The search strategy identified 879 titles and abstracts. We include two international and five national guidelines. Four independent authors assessed the methodological quality of included guidelines using the Appraisal of Guidelines for REsearch & Evaluation (AGREE-II) instrument and systematically extracted the guideline recommendations and supporting research evidence.

Main Results

One hundred and fifty-two different recommendations were made. Ten recommendations (7%) were comparable across guidelines. The European Society of Human Reproduction and Embryology was objectively evaluated as the highest quality guideline (methodological quality score: 88/100). There was substantial variation between the supporting evidence presented by individual guidelines for comparable recommendations. Forty-two recommendations (28%) were not supported by research evidence. No guideline followed the standardised guideline development methods (AGREE-II).

Conclusion

There is substantial variation in the recommendations and methodological quality of endometriosis guidelines. Future guidelines should be developed with reference to high quality methods, in consultation with key stakeholders, including women with endometriosis, ensuring their scope can truly inform clinical practice and eliminate unwarranted and unjustified variations in clinical practice.

Funding

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Keywords

[1] Clinical practice guidelines[2] Diagnosis

[3] Endometriosis [4] Systematic review

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Tweetable abstract

#endometriosis guidelines vary in recommendations and quality. @EndometriosisUK

Introduction

Endometriosis is a benign gynaecological disease characterised by pain and subfertility associated with substantial reductions in quality of life.[1] The disease has three common manifestations: (1) peritoneal endometriosis; (2) ovarian endometriosis; and (3) deep infiltrating endometriosis. The disease was first described in 1860 yet the aetiology and pathogenesis remain poorly understood.[2] Treatment strategies vary significantly between disease severity and the presenting symptoms of pain and / or subfertility.[3] These challenges have resulted in multidirectional research with difficulties producing accurate diagnostic tests or effective therapeutic interventions due to variation and lack of co-ordination along the research pipeline.[4] This variation limits the comparability of research to inform patient care through evidence synthesis in the context of guideline formation and patient information.[5]

Guidelines are systematically developed statements based on the synthesis of best research evidence.[6] Their purpose is to improve patient care by informing clinical practice, reducing unwarranted variations in care, expediting the implementation of effective interventions, and eliminating ineffective interventions.[7,8] The generation of robust guideline recommendations requires standardised guideline development methods, including stakeholder engagement, quality assessment of research evidence, and consensus methods. The methodological quality of guidelines has been reported to be inconsistent.[9-11] Appropriate methodologies and rigorous strategies in the guideline development process are important for the successful implementation of the guideline recommendations.[12-13] Previous comparisons of national endometriosis guidelines were limited by scope, setting, and did not map recommendations and supporting evidence across individual guidelines.[14]

We evaluated the methodological quality of endometriosis guidelines, mapped their recommendations, and explored the relationships between recommendations and research evidence.

Methods

Sources

A protocol with explicitly defined objectives, criteria for guideline selection, and approaches assessing outcome selection was developed and registered with the International Prospective Register of Systematic Reviews (CRD42016036145). This review is reported in

accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[15] Search terms were generated in consultation with healthcare professionals, researchers, and women with endometriosis. We searched the following sources: (1) EMBASE; (2) Medline; and (3) PubMed from inception to February 2016 (Appendix S1). We used the following search terms: (1) endometriosis; (2) endometrio*; (3) guideline; (4) guidance; and (5) consensus.

Guideline selection

We organised the extracted guidelines and removed duplicates. Two reviewers (M.B. and M.H.) independently screened the full content of guidelines to assess eligibility, using a piloted data extraction tool. Any discrepancies between the reviewers were resolved by discussion. We included guidelines reporting recommendations for practice related to the diagnosis or management of endometriosis. We excluded guidelines for the following reasons: (1) local or regional guideline; (2) non-English language publication; or (3) a more recent guideline available from the same authority.

Guideline Characteristics

Two independent reviewers (M.B, and M.H.) extracted information including: country of origin; year of publication; consensus method; stakeholders involved; disease area examined; description of database search; search terms used; language restriction; dates of searches; inclusion / exclusion criteria; and quality assessment instrument.[16]

Recommendations for clinical practice and supporting research evidence

Two independent reviewers (M.B. and M.H) extracted and mapped the recommendation to five pre-specified domains: (1) diagnosis; (2) medical management for pain; (3) surgical management for pain; (4) medical management for infertility; and (5) surgical management of infertility. References supporting clinical recommendations were retrieved and categorised according to hierarchy of medical evidence: (1) Cochrane review; (2) systematic review; (3) randomised control trial; (4) non-randomised control trial; (5) expert opinion; and (6) no reference. Discrepancies were resolved by discussion. Recommendations with no reference or citing expert opinion were classified as having little or no scientific background.

Assessment of methodological quality

Four reviewers (M.B, J.D, M.H, and E.P.) underwent training in the use of the quality assessment instrument, Appraisal of Guidelines for REsearch & Evaluation II (AGREE-II).[15] Each reviewer independently assessed the quality of all included guidelines using the AGREE-II instrument. This validated assessment instrument contains 23 items grouped into six quality domains with a 7-point Likert scale score anchored between 1 (Strongly disagree) and 7 (Strongly agree) for each item.[17]

In addition, we assessed each guideline against six features of systematic review methodology14: (1) named database search; (2) clearly defined search terms; (3) language restrictions; (4) dates of search; (5) detailed search strategy; and (6) description of an inclusion / exclusion criteria. Discrepancies were resolved by discussion.[16]

Analysis

A total guideline score was calculated by summation of its domains and standardised using a prescribed equation.[17] Guidelines were categorised in to low quality (0-33%), moderate quality (34-66%), high quality (67- 100%).

Tabulation and data

Descriptive statistics were calculated for all domains (Median, range, interquartile range (IQR)). We mapped the data for clinical recommendations, their supporting research evidence, and variation in clinical recommendations. There were no substantial discrepancies between authors in the data extraction of quantitative parameters and we observed high interrater agreement. The tables, appendices and sub-categories of presented information was developed in consultation with researchers, healthcare professionals, and women with endometriosis within an iterative process. We sub-categorised interventions according to the presenting symptom: [1] pain or [2] subfertility. Following this, interventions were further categorised to medical and surgical interventions by: [1] disease severity, [2] disease location, [3] adjuncts to surgical management and [4] alternative treatments.

Results

Guideline search and selection

The search strategy identified 879 titles and abstracts. We screened 583 titles and abstracts following the exclusion of 296 duplicate records (Figure 1). We included two international

and five national guidelines: (1) American College of Obstetricians and Gynecologists (ACOG);[18] (2) Australasian Certificate of Reproductive Endocrinology and Infertility Consensus Expert Panel on Trial Evidence (ACCEPT);[19] (3) Collége National des Gynécologues et Obstétriciens Français (CNGOF) Guidelines for the Management of Endometriosis;[20] (4) European Society of Human Reproduction and Embryology (ESHRE) Management of women with endometriosis;[21] (5) National German Guideline (S2k) Guideline for the Diagnosis and Treatment of Endometriosis (NGG);[22] (6) Society of Obstetricians and Gynaecologists of Canada (SOGC);[23] and (7) World Endometriosis Society (WES) Consensus on current management of endometriosis.[24]

Guideline characteristics

The included guidelines were published between 2006 and 2014.[18-24] Five of the guidelines were applicable to the diagnosis and management of pain and subfertility associated with endometriosis.[18, 20-23] Two guidelines reported narrower scopes: the ACCEPT guideline addressed the management of subfertility associated with endometriosis and the WES guideline made recommendations with regards to the management of endometriosis.[19,24]

Between 15 to 56 individuals were involved in guideline development. Between one and four different stakeholder groups assisted in the development of the included guidelines. Three guidelines were developed in collaboration with women with endometriosis.[21,22,24] Two guidelines did not report the geographical location of their developers [18,20] and one guideline was developed by individuals living in a single country.[23] All guidelines developed

recommendations relevant to high-resource settings only. Two guidelines explicitly defined a consensus development method, including the nominal group technique and modified Delphi method.[19,21] No guideline described a detailed search strategy to identify research evidence for use in recommendation formation. Five guidelines described methods to quality assess the research evidence.[18,19,21,23,24]

Recommendations for clinical practice

One hundred and fifty-two recommendations were identified and arranged into six clinical practice domains: (1) diagnosis (36 recommendations); (2) medical management for pain (30 recommendations); (3) surgical management for pain (39 recommendations); (4) assisted reproductive techniques for infertility (12 recommendations); (5) surgical management of infertility (22 recommendations); and (6) alternative treatments for pain and infertility (13 recommendations).

Ten recommendations (7%) were comparable across included guidelines (Table 2,3 Table S1-4). Recommendations often varied across guidelines, for example, the ACOG and NGG guidelines stated different recommendations regarding the use of adjuvant hormonal therapy following surgical management of endometriosis. The ACOG guideline recommended the use of post-operative gonadotrophin releasing hormone analogues for the treatment of pain while the NGG guideline does not recommend their use.

Thirty-six recommendations regarding the diagnosis of endometriosis were made across included guidelines. Four recommendations were described by all guidelines, including: (1) biomarkers are not recommended for the diagnosis of endometriosis; (2) histological confirmation is recommended for the diagnosis of mild to moderate endometriosis (Table 3); (3) histology is recommended to confirm diagnosis; and (4) transvaginal ultrasound imaging is recommended for the diagnosis of endometrioma (Table S1). Seventeen recommendations citied no research evidence or expert opinion.

Thirty recommendations regarding the medical management of endometriosis were made across guidelines. Three recommendations were described by all guidelines: (1) the combined oral contraceptive pill is recommended for endometriosis associated pain; (2) progestogens are recommended for endometriosis associated pain; and (3) gonadotropin releasing hormone analogues are recommended for endometriosis associated pain (Table S4). The strength of recommendations varied across included guidelines (Table S1). Three recommendations citied no research evidence or expert opinion.

Twenty-one recommendations were made with regard to the surgical management of infertility associated with endometriosis. A single recommendation was described by all guidelines: surgery improves fertility with endometriosis associated subfertility. Four recommendations citied no research evidence or expert opinion (Table S5).

Recommendations relating to complementary and alternative interventions were infrequently discussed. Psychological interventions, for example mindfulness practice, were seldom reviewed (Table S4).

Research evidence supporting recommendations

The number of references cited in each guideline ranged from 0 to 211 (Table S3-5). The total number of Cochrane systematic reviews used within each guideline ranged from 0 to 25 and the number of randomised controlled trials used ranged from 0 to 28. Where available we sought the original references used to generate recommendations and summarised the references and study design (table S3-5).

Assessment of methodological quality

A systematic review was described by the majority of guidelines.[18,19,21-24] No guideline explicitly described all six methodological features (Table 1). Several guidelines reported three features [18,19,23] while the CNGOF guideline reported no features. No guideline reported a detailed search strategy or described an explicit inclusion or exclusion criteria for the evidence they sought.

Four guidelines did not report a consensus method.[18,20,23] Five guidelines [19,21-24] reported the inclusion of multiple stakeholder groups, however only three guidelines clearly reported the inclusion of women with endometriosis in its development.[21,22,24] Quality assessment of

retrieved studies was described by five guidelines, assessment methods included: (1) Grading of Recommendations Assessment, Development, and Evaluation;[21,24] (2) Canadian Task Force on Preventative Health Care;[23] (3) National Health and Medical Research Council;[19] and (4) United States Preventative Services Task Force.[18]

Two guidelines were assessed as high quality,[21,24] four guidelines were assessed as moderate quality,[18,19,22,23] and one guideline was assessed as low quality (Table S2).[20] Guidelines were typically of high quality in the domains of clarity and presentation and scope and purpose. Guidelines were of moderate quality in the domains of stakeholder involvement and rigor of development. Guidelines were of low quality in the domains of applicability and editorial independence.

Discussion

Main findings

There is significant variation in endometriosis guideline quality and recommendations. One hundred and fifty-two unique recommendations were reported across seven guidelines, only ten recommendations were comparable. Nearly a third of recommendations were either unreferenced or supported only by expert opinion. No guideline followed the standardised approach to guideline development described within the AGREE-II guideline. The involvement of women

with endometriosis varied significantly, funding sources and conflicts of interest were poorly described, and there was poor reporting of applicability and editorial independence.

Strengths and Limitations

The strengths of this systematic review include its originality, robust search strategy, and methodological design. To our knowledge, this is the first study to systematically appraise the methodological quality and map the recommendations of endometriosis guidelines. There was good agreement between all four reviewers with discrepancies resolved quickly through discussion. We involved a woman with endometriosis in the design and delivery of our research.

Our empirical evaluation is not without limitations. Methodological scoring has not been definitively associated with applicability and clinical practice implementation.[17,30] We did not calculate weighted kappa to explore agreement between authors as the statistical level of agreement required in health research is unclear and it is not currently recommended by the Cochrane Collaboration.[16,31] We could have considered systematically reviewing the randomised controlled trials and systematic reviews to form a judgement on the appropriateness of guideline recommendations. However, this would be unlikely to yield substantial benefit in the context of the considerable resource allocation required.

Interpretation

Our findings justify the critical appraisal of endometriosis guidelines, especially in an area such as endometriosis management, where diagnosis and treatment strategies are deemed suboptimal.[29] With differences in guideline development methods it is not surprising to find a paucity of comparable recommendations with wide intra-guideline variation in the supporting research evidence. The observations and conclusions of this review are likely to be replicated across our specialty.

Guidelines should be developed by searching, collecting, and collating evidence to make judgements utilising robust consensus methods. The methods to achieve this in an unbiased manner are clearly described in the AGREE-II criteria. Variation in methods to identify and assess the included evidence could contribute to the variation in guideline recommendations. A recent Institute of Medicine report on guideline development and their worth in modern clinical practice highlights widespread methodological limitations in formation.[32] Consumers of endometriosis guidelines should be aware of their shortcomings including lack of stakeholder engagement, varied rigor of development, limited applicability, and suboptimal editorial independence. The development of guidelines without a standardised methodological process will lead to the omission of beneficial therapies, an increase in preventable harm, and suboptimal patient outcomes or experiences.[9]

Guideline development can be prohibited by the availability of research evidence to answer the questions raised.[33] The quality of randomised trials is also variable, with variation in outcome collection and reporting being a serious hindrance to progress in our speciality.[34,35]

The development and use of a collection of well-defined, discriminatory, and feasible outcomes, termed a core outcome set, would help to address these issues.[36,37] The Core Outcomes in Women's and Newborn health (CROWN) Initiative aims to optimise the collection and reporting of comparable data, improving evidence-synthesis within clinical guidelines, to support coherent recommendations.[36] Forty-six core outcomes sets are in development, however, reproductive medicine and benign gynaecology are currently under-represented.[37] A core outcome set for endometrioses is currently in development.[38] Four core outcome sets have been completed including preterm birth.[39, 40]

These findings remain consistent with a previous study reporting the low quality of guidelines for pain associated with endometriosis.[14] Over the last decade, there has been limited progress in the development of endometriosis guidelines. Most guidelines were of low quality for the domain 'applicability'. This domain obtained remarkably low scores, as most guidelines did even not discuss the topics of practical implementation, barriers to application, costs, and auditing criteria. These findings are of concern given the significant resources required to generate an ever-increasing body of guidelines.[41] Future endometriosis guidelines should pay close attention to implementation.

The development of guidelines is a resource intensive process with eight different organisations developing endometriosis guidelines, a more coordinated approach would have clear benefits for professionals, researchers, and women with endometriosis.

A single guideline, following AGREE-II guidelines, would reduce the unwarranted and

unjustified variations in clinical practice, and improve clinical outcomes. We urge guideline development groups to work collaboratively to secure maximum efficiency and quality.[42]

Conclusions

There is substantial variation in the recommendations and methodological quality of endometriosis guidelines. Future guidelines should be developed with reference to high quality methods, in consultation with key stakeholders, including women with endometriosis, ensuring their scope can truly inform clinical practice and eliminate unwarranted and unjustified variations in clinical practice.

Acknowledgements

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Disclosure of Interests

The authors declare no conflicts of interest. The ICMJE disclosure forms are available as online supporting information.

Author Contributions

MH, JMND, CD and CB were involved in the conception and design of the research protocol. MH designed the search strategy. EP, MB and MH undertook the screening of search results, paper retrieval, and study selection. EP, JMND, MB, MH extracted data and assessed the

quality of the guidelines. Tables, figures, and appendices were designed by MH and JMND. Drafts of the manuscript were prepared by MH and JMND. All authors contributed to the drafts and final version of the manuscript and approved the final review.

Ethics

Not applicable

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Table 1. Guideline Characteristics.

Guideline (year)	**Scope**	**Stakeholders (n; location)**	**Consensus method**	**Identification of evidence**	**Quality assessment of evidence**
ACCEPT (2012) [19]	[1] Infertility management [2] Pain management	[1] Healthcare professionals (36; unclear) [2] Women with endometriosis (unclear) [3] Pharmaceutical employees (unclear) [4] Researchers (unclear)	[1] Nominal group technique	Database: [1] Embase [2] Pubmed Search terms: reported Language: English Dates: not reported Detailed search strategy: not reported Inclusion / exclusion criteria: not reported	National Health and Medical Research Council
ACOG (2010) [18]	[1] Infertility management [2] Pain management	Not reported	Not reported	Database: [1] ACOG [2] CENTRAL [3] Medline Search terms: not reported Language: English Dates: 1985 - 2010 Detailed search strategy:	United States Preventative Services Task Force

				not reported Inclusion / exclusion criteria: unclear	
CNGOF (2006) [20]	[1] Diagnosis [2] Infertility management [3] Pain management	Not reported	Not reported	Database: not reported Search terms: not reported Language: not reported Dates: not reported Detailed search strategy: not reported Inclusion / exclusion criteria: not reported	Not reported
EHSRE (2014) [16]	[1] Diagnosis [2] Infertility management [3] Pain management	[1] Healthcare professionals (unclear) [2] Women with endometriosis (1; one country) [3] Pharmaceutical employees (unclear) [4] Researchers (n=14;	[1] Nominal group technique [2] Modified Delphi method	Database: [1] CENTRAL [2] Pubmed Search terms: not reported Language: not reported Dates: Inception –January 2012 Detailed search strategy:	Grading of Recommendations Assessment, Development, and Evaluation (GRADE)

		Europe; nine countries)		not reported Inclusion / exclusion criteria: not reported	
NGG (2014) [21]	[1] Diagnosis [2] Infertility management [3] Pain management	[1] Healthcare professionals (11; unclear) [2] Women with endometriosis (unclear) [3] Pharmaceutical employees (unclear) [4] Researchers (21; Europe; five countries)	Not reported	Database: 1] CENTRAL [2] Medline [3] Pubmed Search terms: not reported Language: not reported Dates: not reported Detailed search strategy: not reported Inclusion / exclusion criteria: not reported	Not reported
SOGC (2010) [22]	[1] Infertility management [2] Pain management	[1] Healthcare professionals (unclear) [2] Women with endometriosis (unclear) [3] Pharmaceutical employees (unclear) [4] Researchers (20;	Not reported	Database: [1] CENTRAL [2] Medline Search terms: not reported Language: English Dates: 1985 - 2010 Detailed search strategy:	Canadian Task Force on Preventative Health Care

		Canada)		not reported Inclusion /exclusion criteria: not reported	
WES (2013) [17]	[1] Diagnosis [2] Infertility management [3] Pain management	[1] Healthcare professionals (unclear) [2] Women with endometriosis (unclear) [3] Pharmaceutical employees (unclear) [4] Researchers (n=56; International; 17 countries)	Unclear	Database: not reported Search terms: not reported Language: English Dates: 1985 - 2010 Detailed search strategy: not reported Inclusion / exclusion criteria: not reported	Grading of Recommendations Assessment, Development, and Evaluation (GRADE)

Abbreviations: ACCEPT: Australasian CREI Consensus Expert Panel on Trial Evidence (2012); ACOG: The American Congress of Obstetricians and Gynecologists (2010); CENTRAL: Cochrane Central Register of Controlled Trials; CNGOF: Collège National des Gynécologues et Obstétriciens Français (2006); ESHRE: European Society of Human Reproduction and Embryology (2014); NGG: National German Guideline: Guideline for the Diagnosis and Treatment of Endometriosis (2014); SD: Standard deviation; SOGC: The Society of Obstetricians and Gynaecologists of Canada (2010); WES: World Endometriosis Society (2013).

Table 2. Guideline recommendations for the diagnosis of endometriosis.

Guideline	Mild / moderate endometriosis					Severe endometriosis					Endometrioma				
	Symptoms	Examination	Imaging	Biochemical	Surgical	Symptoms	Examination	Imaging	Biochemical	Surgical	Symptoms	Examination	Imaging	Biochemical	Surgical
ACOG (2010)[18]	•			•	•	•		•					•		
CNGOF (2006)[19]		•	•	•	•		•	•				•	•		
ESHRE (2014)[16]	•	•		•	•		•	•		•		•	•		•
NGG (2014)[21]			•	•	•		•	•				•	•	•	•
SOCG (2010)[22]	•	•	•	•	•	•	•	•	•			•	•	•	•

• Recommendations

World Endometriosis Society (2013) [17] and Australasian CREI Consensus Expert Panel on Trial Evidence (2012) [19] provide no recommendations for the diagnosis of endometriosis.

Table 3. Level of evidence supporting recommendations.

Example 1. Biomarkers should not be used to diagnose endometriosis.

Guideline \ **Level of evidence**	Cochrane review	Systematic review	Randomized trial	Non randomized trial	Expert opinion	No reference	Recommendation stated
ACOG (2010)[18]				•			
CNGOF (2006)[20]						•	
ESHRE (2014)[16]		•					
NGG (2014)[21]		•					
SOCG (2010)[22]		•					

Example 2. Diagnostic laparoscopy and histopathology should be used to diagnose endometriosis.

Guideline \ **Level of evidence**	Cochrane review	Systematic review	Randomized trial	Non randomized trial	Expert opinion	No reference
ACOG (2010)[18]						•
CNGOF (2006)[20]						•
ESHRE (2014)[16]					•	
NGG (2014)[21]		•	•	•		
SOCG (2010)[22]						•

* World Endometriosis Society (2013) [17] and Australasian CREI Consensus Expert Panel on Trial Evidence (2012) [19] provide no recommendations for the diagnosis of endometriosis.

Figure 1. Flow of included guidelines.