Clinical Practice Guideline for the Diagnosis of Endometriosis in the Philippines (Protocol)

Endometriosis CPG Guideline Development Group of the Philippine Society for Reproductive Medicine

I. Scope

Topic

Endometriosis is a common chronic inflammatory condition affecting roughly 10% of reproductive aged women and girls worldwide[1]. Due to its diverse symptoms, diagnosis of endometriosis remains a challenge and continues to cause significant delays and misdiagnoses. Current practice standards, which rely primarily on histopathologic diagnosis before initiating therapy, frequently result in prolonged delay between symptom onset, diagnosis and subsequent treatment. Given the burden and negative impact of endometriosis on the health and well-being of those affected by the disease, improving the standard of care for endometriosis diagnosis is well past due. The scope of this proposed Clinical Practice Guideline (CPG) is to review all available clinical and diagnostic techniques that may reduce the delay in diagnosis of endometriosis and hence bring more rapid relief to affected patients, limit disease progression, and prevent sequelae.

Background and Context

The impact of endometriosis, particularly pain symptoms and infertility, has been shown to significantly affect quality of life in women with the condition. Research has demonstrated the association between endometriosis and mental illness. In addition, endometriosis has a bearing on society in general, through direct and indirect healthcare costs which are comparable to other common chronic diseases such as type 2 diabetes and hypertension[2]. Despite all of these, there is still a need for improving many aspects of the diagnosis of the disease among primary care physicians and other non-specialists to decrease the gap between the onset of symptoms and a reliable diagnosis, referral and treatment.

Many factors such as culture, disease complexity and compromised access to health care likely fuel diagnostic delay and are exacerbated by lack of awareness among the public and clinicians. Worldwide, estimates of diagnostic delay range from 4 to 11 years[3]. A cross-sectional study of 30,000 women in Canada reported an average 5.4-year diagnostic delay of women with endometriosis, with an average 3.1-year delay from onset of symptoms to physician consultation and a 2.3-year delay between physician consultation and diagnosis[3]. This delay in diagnosis may result in prolonged suffering, and worse health-related quality of life for women with endometriosis.

Rationale

There is an urgent need for early recognition of the symptoms of endometriosis, especially among adolescents and young women. All health providers as well as the general public should be made aware of the signs of the disease and recommend further testing to those most likely to have the condition. Diagnosis using non- invasive methods allows for early empiric therapy and has a potential to prevent future morbidities associated with endometriosis especially to limit the development of chronic pelvic pain syndrome. In line with this, the Philippine Society for Reproductive Medicine (PSRM) Research Committee organized a group for the development of a CPG for the diagnosis of endometriosis.

Goal and Objectives

The main objective of the CPG is to determine the accuracy of current noninvasive diagnostic

modalities in comparison with surgical histological confirmation in the diagnosis of endometriosis.

Specific Objectives

1. to determine the accuracy of pelvic examination in the diagnosis of endometriosis
2. to determine the accuracy of sonography in the diagnosis of endometriosis
3. to determine the accuracy of pelvic MRI in the diagnosis of endometriosis
4. to determine the accuracy of tumor markers in the diagnosis of ovarian carcinoma in patients with endometriosis
5. to determine the accuracy of a screening questionnaire in the diagnosis of endometriosis

Expected Target Users and Institutions

This CPG is intended for healthcare professionals attending to females presenting with pelvic pain and/or infertility who may have endometriosis, such as primary care practitioners, general obstetrician gynecologists, reproductive medicine specialists, and the trainees of these specialties. This guideline is also intended for patients with endometriosis and their families, policy makers and the public.

Related Guidelines

In 2008, PSRM released a compilation of consensus statements on endometriosis followed by a CPG on endometriosis in 2014. Both publications included recommendations for diagnosis and management of endometriosis. Eleven years after the last CPG on endometriosis and with numerous new emerging evidence, the Research Committee of PSRM saw the need for a dedicated CPG on the diagnosis of endometriosis, this time focusing on new clinical questions not previously addressed.

Working Groups

A Guideline Development Group (GDG) will be assembled consisting of a multidisciplinary team including clinicians, epidemiologists, public health experts, and patient representatives.

All members of the GDG will undergo Conflict of Interest (COI) review and identified potential COIs will be managed accordingly.

Review Committee:
- Chair
  - Doris R. Benavides, MD
- Members:
  - Maria Lora Palo Garcia-Tansengco, MD
  - Zenith DLT. Zordilla, MD
  - Jovilla M. Abong, MD

Steering Committee:
- Chair
  - Dr. Marian Capco Dichoso (Obstetrics-Gynecology, Reproductive Medicine Specialist)
- Co-Chair
  - Dr. Ester M. Iligan (Pediatrics, Adolescent Medicine Specialist)
- Members:
  - Dr. Joanne Karen S. Aguinaldo (Obstetrics- Gynecology)
  - Dr. Florinda U. Canuto (Family Medicine)

Consensus Panel (representations):
- Philippine Society of Reproductive Medicine
- Pediatric and Adolescent Gynecology Society of the Philippines
- Philippine Society of Ultrasound in Obstetrics and Gynecology
- Philippine Society for Urogynecology and Reconstructive Pelvic Surgery
- Philippine Pediatric Society Inc
- Philippine Academy of Family Physicians
- Philippine College of Emergency Medicine
- Philippine Society of General Surgeons
- Philippine Society of Pediatric Surgeons
- Philippine Society of Colon and Rectal Surgeons
- Philippine Urological Association
- Philippine College of Radiology
- Pain Society of the Philippines
- Philippine Psychiatric Association
- Department of Health
- Health Maintenance Organization
- Philippine Health Insurance Corporation (PhilHealth)
- Patient representatives

Evidence Reviewers:
- Technical Adviser:
  - Marie Carmela M. Lapitan, MD

- Evidence Reviewers:
  - Ina S. Irabon, MD
  - Mona Ethellin Yiu-Senolos, MD
  - Ma. Isidora Margarita Yap-Garcia, MD
  - Alma Joy Bitera-Morin, MD
  - Marie Janice Alcantara-Boquiren, MD
  - Gia C. Pastorfide, MD
  - Leonila Estole-Casanova, MD
  - Maria Delina De Chavez-Nueva, MD
  - Joan Tan Garcia, MD
  - Leedah Ranola-Nisperos, MD
  - Ednalyn T. Ong-Jao, MD
  - Susana S. Lao, MD
  - Debby P. Songco, MD
  - Margaret Joyce Cristi-Limson, MD
  - Angela S. Aguilar, MD
  - Darlene R. Pecache, MD

- Technical Writer:
  - To be determined

Conflicts of Interest

All members of the GDG accomplished and submitted their respective COI declaration forms and curriculum vitae to the COI Review Committee. Each member is expected to declare any conflicts of interest before starting work on the guideline and after 6 months from the onset of the project. (Appendix A)

Guidelines on COI management are as follows:

1. The Steering Committee Chair should have no direct financial COI or relevant indirect non-financial COI.

2. Members of the Steering Committee should have no direct financial COI but may have indirect relevant non-financial COI.

3 No member deciding on the direction and strength of a recommendation should have a direct financial COI.

4. Evidence reviewers with relevant financial and non-financial COIs for a particular guideline question topic are not allowed to review such question.

Key Clinical Questions

Initial priority topics were identified by the Steering Committee and rated them based on disease burden, urgency, clinical practice variation and gaps in health care delivery. After careful consideration and prioritization, the Steering Committee agreed on 5 research questions for the guideline on the diagnosis of endometriosis. The clinical questions were refined following the Population, Intervention, Comparison, and Outcome (PICO) framework.

- *GUIDELINE QUESTION 1: In females suspected of having endometriosis, should a digital rectovaginal exam be performed to diagnose the condition?*

Population	Females suspected of having endometriosis
Intervention	Digital rectovaginal examination
Comparison	• Surgery (laparotomy and laparoscopy) with tissue biopsy • Ultrasound (transrectal, transvaginal, transabdominal, pelvic)
Outcomes	Diagnosis of endometriosis
Subgroups (if any)	• Pediatric • Adult
Remarks / Rationale	A digital rectovaginal exam is part of physical examination of patients seeking consult due to pelvic pain or infertility. However, the exam alone may be insufficient to confirm diagnosis of endometriosis

- *GUIDELINE QUESTION 2: In females suspected of having endometriosis, should a transvaginal/ transrectal/pelvic/ transabdominal ultrasound be performed to diagnose the condition?*

Population	Females suspected of having endometriosis
Intervention	Ultrasound (transrectal, transvaginal, transabdominal, pelvic)
Comparison	Surgery (laparotomy and laparoscopy) with tissue biopsy
Outcomes	Diagnosis of endometriosis
Subgroups (if any)	• Pediatric • Adult
Remarks / Rationale	The gold standard for diagnosing endometriosis is laparoscopy with tissue biopsy however this is invasive and costly. Other non-invasive diagnostic approach such as sonography, paired with clinical symptoms and thorough physical examination, can be useful in diagnosing endometriosis.

- *GUIDELINE QUESTION 3: In females suspected of having endometriosis, should MRI be performed to diagnose the condition?*

Population	Females suspected of having endometriosis
Intervention	MRI
Comparison	Surgery (laparotomy and laparoscopy) with tissue biopsy
Outcomes	Diagnosis of endometriosis
Subgroups (if any)	• Pediatric • Adult
Remarks / Rationale	Although definitive diagnosis of endometriosis is made through laparoscopy with tissue biopsy, MRI can be a valuable tool in diagnosing endometriosis, particularly deep infiltrating endometriosis. MRI can provide detailed images of the pelvis, show location and size of endometriotic growths and help in planning a surgical approach.

- *GUIDELINE QUESTION 4: Should tumor markers (CA 125 and/or HE 4) be performed to diagnose ovarian cancer in females suspected of having endometrioma?*

Population	Females suspected of having endometriosis
Intervention	Tumor markers
Comparison	Surgery (laparotomy and laparoscopy) with tissue biopsy
Outcomes	Diagnose/rule out ovarian cancer
Subgroups (if any)	
Remarks / Rationale	Ovarian carcinoma is a common differential diagnosis for endometriosis, especially in older women. Although tumor markers can be used to distinguish between ovarian carcinoma and endometriosis, their accuracy may be limited.

- *GUIDELINE QUESTION 5: In females suspected of having endometriosis, should a validated questionnaire be used to diagnose the condition?*

Population	Females suspected of having endometriosis
Intervention	Validated questionnaire
Comparison	No checklist
Outcomes	Diagnose endometriosis
Subgroups (if any)	• Pediatric • Adult
Remarks / Rationale	A simple score based on a patient questionnaire could help shorten the time involved in reaching a diagnosis of endometriosis and improve the management and the quality of life of patients.

II. Evidence Review

Systematic Review Methods

The main strategies to identify potentially relevant literature will be through electronic database searching and use of literature recommended by members of the GDG.

An systematic literature search for existing CPGs and diagnostic accuracy studies will be done using MEDLINE through PubMed (https://pubmed.ncbi.nlm.nih.gov/), the Cochrane Library, Embase, Global Index Medicus, Google Scholar), local databases (Herdin and DOH website), and websites of international and local specialty societies. Keywords for the systematic literature search will be derived from the PICO framework for each clinical question, utilizing both MeSH terms and free-text searches. (When necessary, EREs will contact authors of relevant studies to obtain copies or clarify study details for appraisal.

Inclusion and Exclusion Criteria

A clear criteria for including or excluding studies will be adapted for each clinical question to ensure that the evidence is relevant to the guideline question. Since the guideline questions are diagnosis-related, aside from randomized controlled trials (RCTs), cross-sectional (simple or criterion-referenced), cohort, case-control studies, and diagnostic systematic reviews and meta-analyses will also be used.

Included studies will be limited to those involving females suspected with endometriosis, involving the diagnostic accuracy of the tests in question, and involving the considered standard or gold standard tests as comparators. Studies that do not involve the above-mentioned populations, tests and comparators; studies not in English, and where full text and references are not available will not be included in the review.

Quality Assessment of the Studies

Critical appraisal and Risk of Bias assessments of the gathered studies will be done by at least two independent expert reviewers. The QUADAS-2 (for diagnostic accuracy studies) will be used to

assess the risk of bias. The AGREE II (Appraisal of Guidelines for Research & Evaluation) tool will be used to evaluate the quality of the identified guidelines.

Data Extraction and Evidence Retrieval

A customized data extraction form will be used to systematically collect data from each chosen study. The extracted data will include the study design and setting, sample size and population characteristics, and details of the diagnostic test and comparator. Key outcomes such as accuracy, specificity and sensitivity of each diagnostic outcome will also be recorded. Two reviewers will extract data independently, and any discrepancies will be resolved through discussion by a third reviewer.

Synthesis of Evidence

Pooled effect estimates will be calculated using Meta-DiSc 2.0 web application to assess diagnostic test accuracy from multiple studies.

Quality Assessment of the Body of Evidence

The evidence reviewers will rate the overall certainty of evidence using the GRADE approach which will later be presented to the consensus panel. The rating of importance of outcomes into critical, important, or relevant will be decided on by the multi-sectoral consensus panel.

The initial rating of certainty of evidence will be 'high' for RCTs.. For RCTs, the initial 'high' rating may be downgraded if there are issues such as high risk of bias, inconsistency, indirectness, imprecision, and publication bias. Similarly, NSRIs for diagnostic studies will also first be rated as "high" and downgraded based on the same parameters mentioned above.

III. Evidence to Recommendations

Basic Policy for Formulating Recommendations

The gathered evidence will be translated into actionable recommendations. The GRADE approach and the Evidence to Decision Framework will consider factors such as quality of evidence, balance of benefits and harms, patient acceptability and resource availability to determine the direction of the recommendation.

The preliminary strength of recommendation will be determined based on the overall certainty of evidence per guideline question. A high or moderate certainty of evidence will equate to a 'strong' recommendation, while a low or very low certainty will result in a 'weak' recommendation.

A consensus panel will be formed to finalize the recommendations. A consensus is defined by at least 75% agreement among the voting consensus panel members. At least 3 rounds of voting may be done to reach a consensus. On occasions when there are disagreements in voting, the consensus panel members may be asked to explain their votes. In the absence of a consensus after 3 rounds, the committee will proceed to a delphi process for the final recommendation.

Writing the CPG

Once the recommendations are finalized and graded, the guideline will be organized into a clear and logical format which is accessible to the intended users. A technical writer will be commissioned to finalize the CPG that will be approved by the steering committee. The guideline will be reviewed externally and revised accordingly, incorporating the reviewers' inputs.

IV. Implementation

Dissemination

The CPG will be disseminated through multiple channels, such as publications, professional networks, conferences, lectures, and medical society websites. The CPG will be submitted to the DOH for adaptation and uploading on the DOH website. A manuscript containing the CPG development process and recommendations will also be submitted for publication in local journals.

Updating

Regular updates to incorporate new evidence and maintain the guidelines' relevance and accuracy will be done every 3 to 5 years or earlier if there is rapidly evolving evidence.

V. Logistics and Resources

Funding Sources: Philippine Society of Reproductive Medicine
Budget:

Particulars	Details (Quantity, Rate, Duration, etc.)	Amount
I. Personnel Services (PS)		
Honoraria	*Technical lead: 130, 000 pesos* *COI reviewers: 120, 000 pesos* *Technical writer: 50, 000 pesos*	*300, 000 pesos*
II. Operating Expenses		
1. Venue for meetings (including food/travel expenses)	*Steering Committee meetings: 50, 000 pesos* *Evidence Review Experts meetings: 80, 000 pesos* *Consensus Panel meeting: 100, 000 pesos*	*230, 000 pesos*
2. Incidental expenses	*25,000 pesos*	*25, 000 pesos*
Grand Total		**555, 000 pesos**

Timeline:

Month	Month 1	Month 2	Month 3	Month 4 -5	Month 6	Month 6
Activity	Formation of CPG Development Group	Steering committee meeting Nomination of topic and research questions	ERE meeting with technical adviser	Review of literature and formation of initial recommendations to research questions	Consensus Panel Meeting	

References

1. World Health Organization. Endometriosis [Internet]. World Health Organization. 2023. Available from: https://www.who.int/news-room/fact-sheets/detail/endometriosis
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3. Singh S, Soliman AM, Rahal Y, Robert C, Defoy I, Nisbet P, et al. Prevalence, symptomatic burden and diagnosis of endometriosis in Canada: Cross-sectional survey of 30 000 women. J Obstet Gynaecol Canada 2020 Jul; 42(7): 829–38.
4. De Corte P, Moritz Klinghardt, von Stockum S, Heinemann K. Time to diagnose endometriosis: Current status, challenges and regional characteristics—A systematic literature review. J Obstet Gynaecol 2024 Oct 7;132(2).
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7. Wróbel M, Wielgos M, Laudanski P. Diagnostic delay of endometriosis in adults and adolescence-current stage of knowledge. Adv Med Sci 2022 Mar; 67(1):148–53.
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	Please Refer to Annex 2
Timeline	Please Refer to Annex 3

Appendix A.

Endometriosis Clinical Practice Guidelines
Guideline Task Force

Declaration of Conflict of Interests Form

PERSONAL INFORMATION						
CPG Title	**ENDOMETRIOSIS CLINICAL PRACTICE GUIDELINES**					
Name						
Designation						
Institution						
Mobile No.						
Email Address						
CPG Group						
Function/ Role		Steering Committee		Evidence Review Experts		Consensus Panel

POLICY ON COI

1. You have been invited to participate in this CPG development project because of your professional standing and expertise.
2. You must disclose any circumstance that could represent a potential conflict of interest.
3. You must disclose on this Declaration of Conflict of Interests Form any financial, professional, or other interest relevant to the subject of the CPG in which you been asked to participate in or contribute towards, and any interest that could affect the outcome of the project.
4. This declaration form must be completed before participation in the CPG project activity can be confirmed. Another form should be accomplished 6 months after the start of CPG development. The period covered will include 1 year prior to the start of CPG development to the next year.
5. Answering "YES" to a question on this form does not automatically disqualify you or limit your participation in the CPG project. Your answers will be reviewed by an independent COI Review Committee to determine whether you have a COI relevant to the subject of the CPG, and the COI will be managed accordingly.
6. You must promptly inform the reviewers if there is any change in this information prior to or during the course of your work on the CPG project.
7. Incomplete disclosure of all relevant information on this form may, depending on the circumstances, lead the reviewers to decide not to appoint you to future CPG development projects.
8. This declaration applies only to current conflicts of interests (within the past 1 year). It does not apply to past interests that have expired, no longer exist, and cannot reasonably affect current behavior.

CONFLICT OF INTEREST STATEMENT

Please answer each of the questions below. If the answer to any of the questions is "YES", briefly describe the circumstances. The term "YOU" refers to yourself. If you do not describe the nature of an interest, the conflict will be assumed to be significant.

Items	YES	NO	Type	Name of company, organization or institution	Amount of Income or Value of Interest	Period
1. **EMPLOYMENT AND CONSULTING**: Within the past 1 year, have you received remuneration from a commercial entity or other organization with an interest related to the subject of the CPG?						
a. Employment						
b. Consulting (as technical or other advisor)						
2. **RESEARCH SUPPORT**: Within the past 1 year, have you received support for research from a commercial entity or other organization with an interest related to the subject of the CPG?						
a. Research support, including grants, collaborations, sponsorships, and other funding						
b. Non-financial support valued – equipment, facilities, research assistants, paid travel to meetings, etc.						
c. Support (including honoraria) for being on a speakers' bureau, and/or giving speeches or training for a commercial entity or other organization with an interest related to the subject of the CPG						
3. **INVESTMENT INTERESTS**: Do you have investments in any commercial entity with an interest related to the subject of the CPG? (Please also include indirect investments such as a trust or holding company. You may exclude mutual funds, pension funds, or similar investments that are broadly diversified and over which you exercise no control.)						
a. Stocks, bonds, stock options, other securities (e.g. short sales)						

Items	YES	NO	Type	Name of company, organization or institution	Amount of Income or Value of Interest	Period
b. Commercial business interests (proprietorships, partnerships, joint ventures, board memberships, controlling interest in a company)						
4. **INTELLECTUAL PROPERTY**: Do you have any intellectual property rights that might be enhanced or diminished by the outcome of the CPG?						
a. Patents, trademarks, copyrights (including pending applications)						
b. Proprietary know-how in a substance, technology or process						
5. **NON-FINANCIAL INTERESTS**: Are you engaged in any professional or other activities which outside parties could consider might represent or give rise to a conflict of interest, or the perception of a conflict off interest with regard to your CPG work?						
a. Author/ co-author of a published paper related to the CPG topic						
b. Senior editorial role or assignment						
c. Official function in a government agency or international organization						
d. Advisory committee associated with a public or private sector organization						
e. Board member of a public or private sector organization						
f. Board member of a non-profit organization						
g. Board member of an advocacy group						

Items	YES	NO	Type	Name of company, organization or institution	Amount of Income or Value of Interest	Period
6. PUBLIC STATEMENTS AND POSITIONS (during the past 1 year)						
a. Have you given expert testimony (with regard to any regulatory, legislative, or judicial process) related to the subject of the CPG, for a commercial entity or other organization?						
b. Have you held an office or other position, paid or unpaid, where you represented interests or defended a position related to the subject of the CPG?						
7. ADDITIONAL INFORMATION						
a. If not already disclosed above, have you worked for the competitor of a product that is the subject of the CPG, or will your participation in this project or work enable you to obtain access to a competitor's confidential proprietary information, or create for you a personal, professional, financial, or business competitive advantage?						
b. To your knowledge, would the outcome of this CPG project or work benefit or adversely affect interests of others with whom you have substantial						

common, personal, professional, financial, or business interests (such as your adult children or siblings, close professional colleagues, administrative unit or department)?						
c. Excluding this CPG project, has any person or entity paid or contributed towards your travel costs in connection with this work?						
d. Have you received any payments (other than for travel costs) or honoraria for speaking publicly on the subject of this CPG or work?						
e. Is there any other aspect of your background or present circumstances not addressed above that might be perceived as affecting your objectivity or independence?						

8. TOBACCO OR TOBACCO PRODUCTS (answer without regard to relevance to the subject of the meeting or work: Within the past 1 year, have you had employment or received research support or other funding from, or had any other professional relationship within an entity directly involved in the production, manufacture, distribution or sale of tobacco or tobacco products or representing the interests of any such entity?	YES	NO

Consent to Disclosure
By completing and signing this form, you consent to the disclosure of any relevant conflicts to other CPG group members and in the final CPG manuscript.

Declaration
I hereby, declare on my honor, that the disclosed information is true and complete to the best of my knowledge and belief.
Should there be any change to the above information, I will promptly notify the responsible staff of the facilitating agency for CPG development and complete a new declaration of conflict of interest form that described the changes. This included any change that occurs before or during the meeting or work itself and through the period up to the publication of the final CPG manuscript or completion of the activity concerned.

_____ _____
Date Signature Over Printed Name