Endometrial sampling tests for the diagnosis of endometrial carcinoma: a protocol of a diagnostic test accuracy systematic review

Noha Abd Elsattar¹, Marwa Abd Elmawla¹, Somia Labib¹, Menna Kamel², Ashraf Nabhan^{1,2*}

Abstract

Background: Endometrial cancer ranks as the most common gynecological cancer. An accurate detection can dramatically improve patient relevant outcomes.

Objectives: To determine the diagnostic accuracy of different endometrial sampling methods for detecting endometrial carcinoma and its precursors.

Search strategy: we will search the Cochrane library, Pubmed/MEDLINE, Web of Science, and Scopus. We will search references of relevant studies.

Selection criteria: We will include diagnostic test accuracy studies if women had an endometrial sampling followed by verification with histopathology in hysterectomy specimens. The primary target is endometrial carcinoma.

Data collection and analysis: Two authors will independently screen studies, extract data, and assess methodological quality. We will use bivariate diagnostic random-effects meta-analysis.

Results: This is a protocol of a diagnostic test accuracy systematic review.

Conclusions: Evidence will aid in making well-informed decisions for diagnosing endometrial carcinoma. Implications for research will be outlined for future studies.

Keywords

Endometrial sampling; Endometrial carcinoma; Sensitivity; Specificity; Diagnostic accuracy

¹ Department of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, Egypt

² Egyptian Center for Evidence Based Medicine, Egypt

*Corresponding author: anabhan@med.asu.edu.eg

Contents

1	Introduction	1
2	Methods	2
2.1	Eligibility criteria	2
2.2	Information sources	2
2.3	Study selection	2
2.4	Data collection process	2
2.5	Risk of bias and applicability	2
2.6	Synthesis of results	2
3	Results	3
4	Discussion	3
5	Appendices	3

1. Introduction

Endometrial cancer remains a major health concern. It ranks as the most common gynecological cancer and as the 14th leading cause of death from cancer in women. [1–3]

Most cases affect postmenopausal women [4] and postmenopausal bleeding (PMB) is the most frequent symptom of endometrial cancer. [5] It is, however, a non-specific marker of the disease. While 90 percent of women with endometrial cancer initially present with PMB, only 5 to 10 percent of women with PMB are diagnosed with endometrial cancer. [5] Irregular pre- or peri-menopausal bleeding remains an important presenting symptom. Endometrial cancer is sometimes diagnosed in women without an abnormal uterine bleeding. This occurs during the investigation of a thick endome-

trial line found on an imaging technique performed for other reasons or incidentally in hysterectomy specimens performed for benign conditions. [3, 6]

Survival from endometrial cancer depends on the stage at diagnosis. By enabling an early detection of atypical hyperplasia and early-stage endometrial cancer, an accurate early detection will dramatically improve outcomes. [3, 7, 8]

The aim of this systematic review and meta-analysis is to determine the diagnostic accuracy of different endometrial sampling tests for detecting endometrial carcinoma and its precursors.

2. Methods

We will conduct the systematic review using methodological approaches pre-specified in this protocol. We prospectively registered the protocol in PROSPERO and OSF Registries (<https://osf.io/h8e9z>). We will report the review according to the Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies (PRISMA-DTA) guidelines. [9].

2.1 Eligibility criteria

We will include published cross-sectional studies that have evaluated the diagnostic accuracy of different endometrial sampling methods, followed by verification of study participants with a reference test. Participants are women who underwent endometrial sampling. Index tests include different endometrial sampling techniques. Target conditions included endometrial hyperplasia or carcinoma. We will accept histopathology of hysterectomy specimens as the reference standard for the diagnosis of the target conditions. We will exclude studies of a case-control design as these are considered to have high risk of bias due to inflated accuracy estimates.

2.2 Information sources

We will use a comprehensive search strategy to find published articles (Appendix 1). We will search the Cochrane library, Pubmed/MEDLINE, Web of Science, and Scopus. We will not apply any restrictions on language or date of publication. Strategies will utilize a combination of controlled vocabulary and keywords. Pubmed search strategy is detailed in Appendix 1.

Searching other resources We will search the reference lists in articles retrieved from electronic databases and relevant review articles.

2.3 Study selection

Two review authors will use a reference manager to import and de-duplicate search results.

They will independently screen titles and abstracts to identify potentially eligible studies for full-text retrieval. Two review authors will double check the list of potentially eligible studies.

Review authors working in pairs, will independently assess the full text using the predefined eligibility criteria.

They will resolve discrepancies by discussion and by consulting with the lead author.

2.4 Data collection process

For each included study, two review authors will independently extract the following data: General information: title, journal, year, and study design; Sample size: total number of participants included and tested; Baseline characteristics: age, index test, threshold for the definition of a positive screening result; reference test; numbers of true positive, true negative, false positive, and false negative findings.

We will extract these data for both target conditions. All numbers will be double checked by two authors. We will summarize the data from each study in 2×2 tables (true positive, false positive, false negative, true negative).

2.5 Risk of bias and applicability

Review authors, working in pairs, will independently assess the risk of bias of included studies and applicability of their results using QUADAS-2 [10]. They will resolve discrepancies by discussion and by consulting with the lead author. We will address aspects of study quality involving the participant spectrum, index tests, target conditions, reference standards, and flow and timing (Appendix 2).

We will classify a study as having a high risk of bias if at least one of the domains of QUADAS-2 was judged as being high risk.

2.6 Synthesis of results

Each method of endometrial sampling will be compared against the reference test. For each method of endometrial sampling, TP, TN, FP, and FN will be computed. We will use bivariate diagnostic random-effects meta-analysis [11]. We will present the results in a summary receiver operating characteristic (ROC) curve. We will

use the Markov chain Monte Carlo procedure to generate summary positive and negative likelihood ratio and diagnostic odds ratio for the bivariate model [12]. When there are three or less studies, we will use a univariate random-effects model.

For each of the target condition, we will present the synthesis by the method of sample collection. We will assess the effect of risk of bias of included studies on diagnostic accuracy by performing a sensitivity analysis in which we will exclude studies classified as having high risk of bias.

We will use R software version 4.1.2 and package ‘mada’ version 0.5.10 [13].

3. Results

We will report the results under the following headings:

1. Study selection
2. Study characteristics
3. Risk of bias and applicability
4. Results of individual studies
5. Synthesis of results
6. Additional analysis

4. Discussion

The review will assess the diagnostic accuracy of different endometrial sampling methods for detecting endometrial cancer. We will consider only cross-sectional studies for inclusion in the review.

We will compute pooled estimates of diagnostic test accuracy of all tests and will present the results by type of test and sample collection procedure.

5. Appendices

Appendix 1: Pubmed search strategy

("endometrial neoplasms"[MeSH Terms] OR "endometrial hyperplasia"[MeSH Terms] OR "endometrial cancer"[tiab] OR "endometrial carcinoma"[tiab] OR "endometrial adenocarcinoma"[tiab] OR "endometrial hyperplasia"[tiab])

AND (sampling[tiab] OR biopsy[tiab] OR biopsies[tiab] OR curettage[tiab] OR Pipelle[tiab] OR Brush[tiab] OR Curette[tiab])

AND ("sensitivity and specificity"[MeSH Terms] OR predict*[tiab] OR diagnos*[tiab] OR accura*[tiab])

Appendix 2: QUADAS-2 tool

1. Domain 1: PATIENT SELECTION A. Signaling questions (yes/ no/ unclear) 1. Was a consecutive or random sample of patients enrolled? 2. Was a case-control design avoided? 3. Did the study avoid inappropriate exclusions? B. Risk of bias: High/ low/ unclear: Could the selection of patients have introduced bias? C. Concerns regarding applicability: High/ low/ unclear: Are there concerns that the included patients do not match the review question?
2. Domain 2: INDEX TEST A. Signaling questions (yes/ no/ unclear) 1. Were the index test results interpreted without knowledge of the results of the reference standard? 2. If a threshold was used, was it pre specified? B. Risk of bias: High/ low/ unclear: Could the conduct or interpretation of the index test have introduced bias? C. Concerns regarding applicability: High/ low/ unclear: Are there concerns that the index test, its conduct, or interpretation differ from the review question?
3. Domain 3: REFERENCE STANDARD A. Signaling questions (yes/ no/ unclear) 1. Is the reference standard likely to correctly classify the target condition? 2. Were the reference standard results interpreted without knowledge of the results of the index test? B. Risk of bias: High/ low/ unclear: Could the reference standard, its conduct, or its interpretation have introduced bias? C. Concerns regarding applicability: High/ low/ unclear: Are there concerns that the target condition as defined by the reference standard does not match the review question?
4. Domain 4: FLOW AND TIMING A. Signaling questions (yes/ no/ unclear) 1. Was there an appropriate interval between index test(s) and reference standard? 2. Did all patients receive a reference standard? 3. Did all patients receive the same reference standard? 4. Were all patients included in the analysis? B. Risk of bias: High/ low/ unclear: Could the patient flow have introduced bias?

Competing interests The author declares no competing interests.

References

- [1] Freddie Bray, Jacques Ferlay, Isabelle Soerjomataram, Rebecca L Siegel, Lindsey A Torre, and Ahmedin Jemal. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, 68(6):394–424, nov 2018.
- [2] Nicole Concin, Carien L. Creutzberg, Ignace Vergote, David Cibula, Mansoor Raza Mirza, Simone Marnitz, Jonathan A. Ledermann, Tjalling Bosse, Cyrus Chargari, Anna Fagotti, Christina Fotopoulou, Antonio González-Martín, Sigurd F. Lax, Domenica Lorusso, Christian Marth, Philippe Morice, Remi A. Nout, Dearbhaile E. O'Donnell, Denis Querleu, Maria Rosaria Raspollini, Jalid Sehouli, Alina E. Sturdza, Alexandra Taylor, Anneke M. Westermann, Pauline Wimberger, Nicoletta Colombo, François Planchamp, and Xavier Matias-Guiu. Esgo/estro/esp guidelines for the management of patients with endometrial carcinoma. *Virchows Archiv : an international journal of pathology*, 478:153–190, February 2021.
- [3] Martin Koskas, Frédéric Amant, Mansoor Raza Mirza, and Carien L. Creutzberg. Cancer of the corpus uteri: 2021 update. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics*, 155 Suppl 1:45–60, October 2021.
- [4] R. Manchanda and S. Thapa. An overview of the main intrauterine pathologies in the postmenopausal period. *Climacteric : the journal of the International Menopause Society*, 23:384–387, Aug 2020.
- [5] J. Carugno. Clinical management of vaginal bleeding in postmenopausal women. *Climacteric : the journal of the International Menopause Society*, 23:343–349, Aug 2020.
- [6] Acog committee opinion no. 734: The role of transvaginal ultrasonography in evaluating the endometrium of women with postmenopausal bleeding. *Obstetrics and gynecology*, 131:e124–e129, May 2018.
- [7] Nehalennia van Hanegem, Marileen M. C. Prins, Marlies Y. Bongers, Brent C. Opmeer, Daljit Singh Sahota, Ben Willem J. Mol, and Anne Timmermans. The accuracy of endometrial sampling in women with postmenopausal bleeding: a systematic review and meta-analysis. *European journal of obstetrics, gynecology, and reproductive biology*, 197:147–155, February 2016.
- [8] Nicole C. M. Visser, Maria C. Breijer, Malou C. Herman, Ruud L. M. Bekkers, Sebastiaan Veersema, Brent C. Opmeer, Ben W. J. Mol, Anne Timmermans, and Johanna M. A. Pijnenborg. Factors attributing to the failure of endometrial sampling in women with postmenopausal bleeding. *Acta obstetrica et gynecologica Scandinavica*, 92:1216–1222, October 2013.
- [9] Matthew D F McInnes, David Moher, Brett D Thombs, Trevor A McGrath, Patrick M Bossuyt, and the PRISMA-DTA Group. Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. *JAMA*, 319(4):388–396, jan 2018.
- [10] Penny F Whiting, Anne W S Rutjes, Marie E Westwood, Susan Mallett, Jonathan J Deeks, Johannes B Reitsma, Mariska M G Loefflang, Jonathan A C Sterne, and Patrick M M Bossuyt. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Annals of internal medicine*, 155(8):529–536, oct 2011.
- [11] Johannes B Reitsma, Afina S Glas, Anne W S Rutjes, Rob J P M Scholten, Patrick M Bossuyt, and Aeilko H Zwinderman. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *Journal of clinical epidemiology*, 58(10):982–990, oct 2005.
- [12] Aeilko H Zwinderman and Patrick M Bossuyt. We should not pool diagnostic likelihood ratios in systematic reviews. *Statistics in Medicine*, 27(5):687–697, feb 2008.
- [13] R Core Team. R: A Language and Environment for Statistical Computing, 2020.