SYSTEMATIC REVIEW

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Comparison between endometrial hyperplasia classifications. Systematic review and quality evaluation

Comparación entre las clasificaciones de hiperplasia endometrial. Revisión sistemática y evaluación de calidad

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ABSTRACT

Background: Endometrial hyperplasia is currently classified into non-atypical or benign hyperplasia and precancerous lesion, atypical hyperplasia/endometrioid intraepithelial neoplasia or EIN, according to two systems, the World Health Organization (WHO) which modified its previous classifications in 2014 -although the 1994 classification is still widely used- and the endometrial intraepithelial neoplasia (EIN) system. It is still unclear which classification system for endometrial hyperplasia should be used for patient management and treatment. Objective: To review and evaluate meta-analyses comparing the World Health Organization classification systems for endometrial hyperplasia and the EIN system. Methods: Systematic review of meta-analysis studies using the search terms "endometrial hyperplasia" in PubMed, Embase and Lilacs databases. The meta-analyses finally selected were scored using the AMSTAR 2 assessment tool. Results: We found 154 articles of which, after selection and complete reading, three were finally extracted for qualitative analysis. The rating of the meta-analyses reviewed with the AMSTAR 2 assessment tool found that the overall confidence of their results was critically low. Conclusions: The data show that objective morphometry in the EIN system is more reliable than the WHO criteria for assessing the risk of progression of endometrial hyperplasia to cancer. Comparison between the WHO system and the subjective EIN system resulted in similar prognostic values. Another meta-analysis showed a clear discrepancy between the 1994 WHO system and the EIN system. Evaluation using the AMSTAR-2 assessment tool showed that the overall confidence in the results of the evaluated studies was critically low.

Key words: Endometrial hyperplasia, Pathology, Classification, World Health Organization.

RESUMEN

Antecedentes. La hiperplasia endometrial se clasifica actualmente en hiperplasia sin atipia o benigna y en lesión precancerosa, hiperplasia atípica / neoplasia intraepitelial endometrioide o EIN, según dos sistemas, el de la Organización Mundial de la Salud (OMS) que modificó sus anteriores clasificaciones en 2014 -aunque la de 1994 sigue siendo muy usada- y el sistema de neoplasia intraepitelial endometrial (EIN). Aún no está claro qué sistema de clasificación de la hiperplasia endometrial debe utilizarse para el control y tratamiento de las pacientes. Objetivo. Revisar y evaluar metaanálisis que comparen los sistemas de clasificación para la hiperplasia endometrial de la Organización Mundial de la Salud y el sistema EIN. Métodos. Revisión sistemática de estudios de metaanálisis utilizando los términos de búsqueda 'hiperplasia endometrial' en las bases de datos PubMed, Embase y Lilacs. Los metaanálisis finalmente seleccionados se calificaron con la herramienta de evaluación AMSTAR 2. Resultados. Se encontraron 154 artículos de los cuales, después de selección y lectura completa, finalmente se extrajeron tres para análisis cualitativo. La calificación de los metaanálisis revisados con la herramienta de evaluación AMSTAR 2 encontró que la confianza general de sus resultados fue críticamente baja. Conclusiones. Los datos muestran que la morfometría objetiva en el sistema EIN es más confiable que los criterios de la OMS para evaluar el riesgo de progresión de la hiperplasia endometrial a cáncer. La comparación entre el sistema de la OMS y el sistema subjetivo de EIN dio como resultado valores pronósticos similares. Otro metaanálisis mostró una clara discrepancia entre el sistema de la OMS de 1994 y el sistema EIN. La evaluación mediante la herramienta de evaluación AMSTAR-2 mostró que la confianza general en los resultados de los estudios evaluados fue críticamente baja.

Palabras clave. Hiperplasia endometrial, Patología, Clasificación, Organización Mundial de la Salud.

Introduction

Endometrial hyperplasia is a spectrum of morphological alterations ranging from benign changes to premalignant disease characterized by hyperplastic changes in the glandular and stromal structures of the endometrium lining the uterine cavity, with a preponderance of an increase in the gland/stromal ratio compared to normal proliferative endometrium[1]. The clinical significance of endometrial hyperplasia lies in the associated risk of progression to endometrioid-type endometrial cancer, with atypical forms of endometrial hyperplasia being considered premalignant lesions[2]. Most cases of hyperplasia result from high estrogen levels with insufficient progesterone levels[3-5]. But some studies have found that atypical endometrial hyperplasia/endometrioid intraepithelial neoplasia (AEH/EIN) emerges as a clonal process that begins as a localized lesion usually in a context of hyperplasia without atypia[6].

Many classifications have been proposed for endometrial hyperplasia. However, the most widely used is the one proposed by the World Health Organization (WHO) in 1994, based on the complexity of the glandular architecture (simple or complex) and on cytological (nuclear) features, such as hyperplasia or atypical hyperplasia[1], determining four categories of endometrial hyperplasia: simple hyperplasia, complex hyperplasia, simple hyperplasia with atypia and complex hyperplasia with atypia[5]. However, this classification has been criticized for its low reproducibility and lack of pathogenic and molecular support[7-10], so an alternative system [endometrial intraepithelial neoplasia (EIN system)] was proposed to improve the differential diagnosis[2,7-9]. The EIN system separates endometrial hyperplasia into benign and EIN according to a combination of morphologic parameters that are objectively or subjectively evaluable[11]. It is based on the nuclear and architectural features of endometrial hyperplasia, which are objectively assessed by computerized morphometric analysis. Analysis of the gland to stroma ratio, glandular perimeter and nuclear diameter allows the calculation of a prognostic score (D score)[7–8] and classifies it as "benign" if the D score ≥ 1, and "EIN" if the D score < 1[2,8,12]. However, D-scoring is not widespread, due to the costs of a morphometry workstation[8]. For a simpler and wider application of such a system, a surrogate subjective evaluation classification of the EIN system was developed. The subjective EIN criteria for precancerous lesion include increased gland to stroma ratio, cytological differences with adjacent endometrium, lesion dimensions, and exclusion of benign conditions simulating endometrial hyperplasia as well as invasive endometrial carcinoma[11].

The 1994 WHO classification was revised in 2003, eliminating the category of simple atypical endometrial hyperplasia, leaving those of simple, complex and atypical endometrial hyperplasia[13,14]. However, given the scientific impact of the EIN system, in 2014 the WHO proposed a dual classification of "without atypia" and atypical, establishing the difference between benign and premalignant (atypical endometrial hyperplasia/endometrioid intraepithelial neoplasia), based on cytological atypia[14]. This classification reports "EIN", which can create confusion, because it is unclear whether it refers to the EIN system mentioned above (although the 2014 WHO classification is not well integrated with the EIN criteria)[14].

The WHO classification system remains the most widely used and reported in the literature, but several institutions prefer the EIN based on several studies supporting better reproducibility and accuracy compared with the WHO system[9,10,15].

Meta-analysis type studies comparing the WHO and EIN system classifications, selected through systematic review, are presented and scored using the AMSTAR 2 tool, which allows critical appraisal of systematic reviews that include randomized or non-randomized studies as well as those with both designs in healthcare interventions[16]. (Appendix A).

Methods

A search for publications was performed using the keywords "Endometrial Hyperplasia" in the databases PubMed and Embase with the meta-analysis and year filters (from 2005 to 2021) and Lilacs, with the key words in Spanish and the systematic review filter, in December 2020 and January 2021. The retrieved articles were screened by title and abstract independently with another reviewer, agreeing to read the full article in case of discrepancy to make the deci-

sion of their choice after reading. The reference lists of the articles identified in this search were also reviewed. The articles selected from this screening were studied by the author with the full article, determining their relevance to the review. The meta-analyses finally extracted were scored using the AMSTAR 2 assessment tool.

Results

The database searches found 154 articles. All of them were screened, selecting five publications for complete review by the author. After this evaluation was completed, three meta-analyses were finally extracted for qualitative analysis (Figure 1).

The two final exclusions (Travaglino et al. (14) and Doherty et al.[17] were made because these meta-analyses did not compare classifications of endometrial hyperplasia.

Some interesting results from the included studies are presented below. The item ratings in the studies analyzed with the AMSTAR 2 assessment tool are presented in Table 1.

In a meta-analysis of studies evaluating endometrial hyperplasia by both the WHO 1994 classification and the EIN system, eight studies (1,352 hyperplasias) were included. The congruence with EIN criteria was fair for non-atypical hyperplasia, 0.241, and moderate for atypical hyperplasia, 0.815[18].

Another study evaluated the reliability of the WHO system, the D-score and the subjective EIN system in grading the risk of progression to cancer in endometrial hyperplasia. Twelve studies were included in the meta-analysis (the one study with high risk of bias was excluded). The pooled RR for progression to cancer in the WHO system had RR of 8.74 (95% CI 6.66-11.47). The objective D-score RR of 29.22 (95% CI 13.24-64.51), significantly higher than that of WHO (p = 0.005). The subjective EIN system with RR of 19.37 (95% CI 5.86-64.01) was intermediate between WHO and D score, with no significant difference (p = 0.20 and p = 0.57, respectively)[12].

Travaglino, et al.[10] reviewed the subjective classifications of endometrial hyperplasia (WHO or EIN) to determine their prognostic value in assessing the risk of coexisting cancer. The WHO criteria showed an OR of 11.15 (95% CI 7.65-16.24), sensitivity of 0.86 (95% CI 0.82-0.90) and specificity of 0.67 (95% CI 0.64-0.70) for coexistent cancer. The subjective EIN system showed a similar OR (11.85, 95% CI 4.91-28.62, p=0.90), higher sensitivity (0.98, 95% CI 0.94-0.99) and lower specificity (0.29, 95% CI 0.24-0.34).

Discusion

The most widely used classification system for endometrial hyperplasia is that proposed by the World Health Organization (WHO) in 1994 and subsequently revised[2,7,9]. The 2014 WHO classification identifies cytologic atypia as the crucial criterion for premalignancy, regardless of the complexity of the architecture[6,10]; it designates atypical endometrial hyperplasia (HA)/endometrioid intraepithelial neoplasia (EIN) as premalignant and endometrial hyperplasia without atypia as benign[6,12].

Figure 1. Flow if information through the different phases of the systematic review.

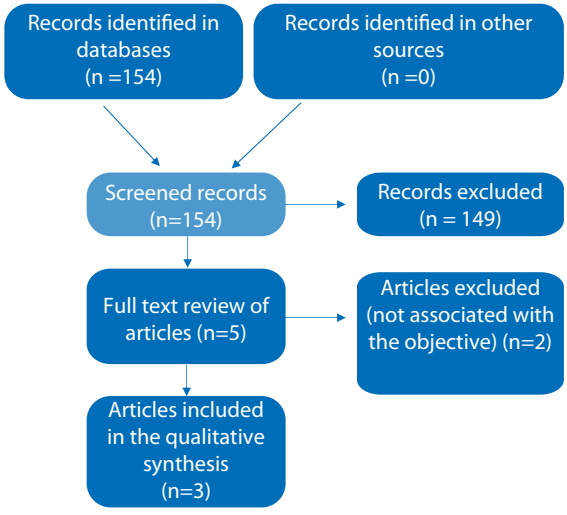

Table 1. Assessment of each domain in the meta-analyses reviewed with the critical appraisal tool for reviews AMSTAR 2[16].

Question / Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Rating
Travaglino et al.[17]	Y	P	N	P	Y	N	N	P	P	N	N	Y	N	Y	N	N	CL
Raffone et al.[12]	Y	P	N	P	Y	N	N	P	P	N	N	Y	N	Y	N	Y	CL
Travaglino et al.[10]	Y	P	N	P	Y	N	Y	P	P	N	N	Y	N	Y	N	N	CL

Y: yes; P: partial yes; N: no. CL: critically low.

The 2014 WHO classification recognized the dual nature of endometrial hyperplasia proposed by the EIN system. The limitation of that classification is that, despite referring to the EIN system, it does not clearly state the changes in the criteria adopted to categorize endometrial hyperplasia, thus leaving cytologic atypia as the only important parameter for recognizing precancerous lesions. However, it has been shown that cytologic changes in precancerous endometrial lesions can be subtle. Therefore, an application of the WHO system based solely on cytologic atypia may miss many of these lesions with a significant risk of progression to malignancy. Conversely, a misdiagnosis of a precancerous lesion may result in overtreatment. The EIN system specifies that the architectural criterion of glandular crowding is necessary for a diagnosis of precancerous lesion and proposes an alternative method for assessing cytologic atypia, based on comparison with the background endometrium rather than absolute criteria[18].

It is still unclear what classification system for endometrial hyperplasia should be used globally to direct patient management[12]. Benign endometrial hyperplasia can be followed without any treatment when it is asymptomatic; otherwise, progestogens can be used. On the other hand, premalignant endometrial hyperplasia requires hysterectomy; in selected cases (desire to preserve fertility, contraindication to surgery), conservative treatment may be chosen, using progestogens alone or together with hysteroscopic resection[13,19,20].

To define whether the 1994 WHO classification can be directly transferred to the EIN system, a meta-analysis was performed[18], finding that the 1994 WHO classification has only a slight concordance with the EIN system: approximately one fourth of the hyperplasia without atypia met the EIN system criteria for premalignant lesion and almost one fifth of the 1994 WHO category of atypical hyperplasia was found to be benign according to the EIN criteria, with moderate concordance. The study concluded that the 1994 WHO classification is not concordant with the EIN system and cannot be directly translated into a dual classification.

The risk of progression to cancer in endometrial hyperplasia was assessed according to the 1994 WHO classification and the EIN system (objective and subjective assessment)[12], concluding that the D-scored EIN criteria were significantly more reliable than the WHO criteria, but the subjective EIN criteria did not show significant superiority over the WHO.

To establish which of the subjective classifications of endometrial hyperplasia (WHO or EIN) has better prognostic value in assessing the risk of coexisting cancer, a study was developed[10] that found similar prognostic values for the WHO system and the subjective EIN system. However, the EIN criteria appear to be more sensitive and therefore more suitable for the initial identification of women in need of treatment, whereas the WHO criteria, based on cytologic atypia, appear to be more specific in predicting the risk of coexistent cancer; therefore, the authors propose that an integration of the EIN system with cytologic atypia should be considered.

The role of biomarkers has also been studied in the classification of endometrial hyperplasia. The 2014 WHO AH / EIN classification contains many of the genetic changes seen in endometrioid-type endometrial carcinoma. These include microsatellite instability, PAX2 inactivation, and mutation of PTEN, KRAS, and CTNNB1 (β-catenin)[6]. However, none of them diagnose the disease or are prognostically useful with sufficient accuracy to be applied in clinical practice[21].

The quality assessments in the meta-analyses evaluated rated the overall confidence in the results of the reviews as critically low according to the AMSTAR 2 tool. This means that the reviews have more than one critical flaw and should not be relied upon to provide an accurate and complete summary of the available studies[16].

Conclusions

Many different classification systems for endometrial hyperplasia have been proposed and included in clinical practice. The 1994 WHO classification represented a major advance in standardizing terminology worldwide, but limitations such as poor reproducibility and lack of pathogenetic and molecular basis promoted the acceptance of the EIN system. Data show that objective morphometry in the EIN system is more reliable than the WHO criteria for assessing the risk of progression of endometrial hyperplasia to cancer. A comparative study between

the WHO system and the subjective EIN system yielded similar prognostic values, although integration of the EIN system with cytologic atypia may perform better. Another meta-analysis showed a clear discrepancy between the 1994 WHO system and the EIN system. Useful biomarkers are needed in clinical practice for the diagnosis and prognosis of endometrial hyperplasia. Evaluation of the meta-analyses with the AMSTAR 2 tool showed that the overall confidence in the results of the evaluated studies was critically low.

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Appendix A

AMSTAR 2. Tool for critical evaluation of systematic reviews in health intervention studies, based on Shea et al. 2017[15].

1. Did the research questions and inclusion criteria for the review include the components of PICO*?
2. Did the report of the review contains an explicit statement that the review methods were established before the conduct of the review and did the report justify any significant deviations from the protocol?
3. Did the review authors explain their selection of the study designs for inclusion in the review?
4. Did the review authors use a comprehensive literature search strategy?
5. Did the review authors perform study selection in duplicate?
6. Did the review authors perform data extraction in duplicate?
7. Did the review authors provide a list of excluded studies and justify the exclusions?
8. Did the review authors describe the included studies in adequate detail?
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?
10. Did the review authors report on the sources of funding for the studies included in the review?
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

**PICO= population, intervention, control group and outcome*