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REVIEW ARTICLE

Complexity of glandular architecture should be reconsidered in the classification and management of endometrial hyperplasia

ANTONIO TRAVAGLINO,[1] ANTONIO RAFFONE,[2] GABRIELE SACCONE,[2] ANTONIO MOLLO,[2] GIUSEPPE DE PLACIDO,[2] MASSIMO MASCOLO,[1] LUIGI INSABATO[1] and FULVIO ZULLO[2]

[1]Anatomic Pathology Unit, Department of Advanced Biomedical Sciences; [2]Gynecology and Obstetrics Unit, Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy

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The 2014 World Health Organization (WHO) classification of endometrial hyperplasia (EH) defines premalignant EH based on only cytologic atypia, disregarding architecture complexity. We aimed to assess the impact of architecture complexity on the risk of cancer in non-atypical EH. A systematic review and meta-analysis was performed by searching electronic databases form their inception to October 2018. All studies assessing the rates of progression to cancer in non-atypical EH (simple vs complex) were included. Pooled relative risk (RR) for cancer progression was calculated; a p-value < 0.05 was considered significant. Eight studies with 1066 women were included. The risk for progression of non-atypical EH to cancer was significantly higher in complex EH than in simple EH ($p < 0.0001$), with an RR of 4.90. In conclusion, the complexity of glandular architecture significantly increases the risk of cancer in non-atypical EH. Complex non-atypical EH may be regarded as a low-risk premalignant lesion rather than a benign condition.

Key words: World Health Organization; endometrial intraepithelial neoplasia; endometrioid adenocarcinoma; endometrial precancer; atypical endometrial hyperplasia.

Antonio Raffone, Gynecology and Obstetrics Unit, Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Via Sergio Pansini, 5, Naples, 80131, Italy. e-mail: anton.raff one@gmail.com

Endometrial hyperplasia (EH) is an irregular proliferation of endometrial glands, which can coexist with or progress to endometrial cancer (1, 2). The risk of cancer is highly variable in EH. Before 2014, the World Health Organization (WHO) classification had considered complexity of glandular architecture and cytologic atypia as the crucial morphologic features in EH, in order to determine the risk of progression to cancer (2–4). The EH had been categorized as 'simple EH without atypia' (S-EH, low risk), 'complex EH without atypia' (C-EH, intermediate risk) or 'atypical EH' (A-EH, high risk) (4).

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However, it has been shown that EH actually has a dual nature: some EH are polyclonal proliferations, reactive to an unopposed action of estrogens, while other EH are monoclonal and constitute the precursor of endometrioid adenocarcinoma (1–3). The differential diagnosis between benign and premalignant EH is crucial for the patient management. Indeed, benign EH may be followed without any treatment when asymptomatic; otherwise, progestins may be used. On the other hand, premalignant EH requires hysterectomy; in selected cases (wish to preserve fertility, contraindication for surgery), a conservative treatment can be chosen, using progestins alone or in combination with hysteroscopic resection (5–7).

The current WHO classification (2014) defines A-EH as a premalignant lesion. On the other hand, EH without atypia is defined as benign, lumping together S-EH and C-EH (1). In spite of this, there is evidence that a significant fraction of C-EH may actually be precancerous lesions (8). Considering these lesions as benign may lead not to treat the patients, with a risk of progression to cancer.

In this study, we aimed to define the prognostic significance of the complexity of EH glandular architecture in the absence of cytologic atypia, by comparing the risk of progression to cancer in S-EH vs C-EH.

MATERIALS AND METHODS

Study protocol

Methods for data collection, risk of bias assessment, data extraction and data analysis were designed *a priori*. All review stages were conducted independently by two reviewers (AT, AR). Disagreements were resolved by discussion with a third reviewer (GS).

The study was reported following the Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) statement (9).

Search strategy

MEDLINE, Scopus, Web of Science, EMBASE, ClinicalTrials.gov, OVID, Cochrane Library and Google Scholar were searched for relevant articles from the inception of each database to October 2018. Several researches were made by using a combination of the following text words found on Medical SubHeading (MeSH) vocabulary: 'endometr*'; 'hyperplas*'; 'intraepithelial neoplasia'; 'precancer'; 'premalignant'; 'precursor'; 'WHO'; 'EIN'; 'WHO'; 'cancer'; 'carcinoma'; 'adenocarcinoma'; 'predict*'; 'prognos*'; 'progress*'; 'develop*'; 'risk'. References from relevant articles were also reviewed.

Study selection

We included all peer-reviewed, retrospective or prospective studies assessing the rates of progression to cancer separately for S-EH and C-EH.

Exclusion criteria, defined *a priori*, were:

1. assessment of only EH that underwent hysterectomy as primary treatment;
2. reviews;
3. same cohort of patients as a study had already included.

Risk of bias within studies assessment

The revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) was used to assess the risk of bias within studies (10). The risk of bias was assessed in each study for four domains: (i) patient selection (if patients were consecutively selected); (ii) index diagnosis (if endometrial sampling was performed with the same method for all patients), (iii) reference diagnosis (if the progression to cancer was confirmed on a subsequent hysterectomy), (iv) flow and timing (if all patients were followed for at least one year, as the EC diagnosed within one year from the index diagnosis are usually considered as 'coexistent' rather than subsequently developed (11, 12)). For each domain, authors' judgments were 'low risk', 'high risk' or 'unclear risk of bias' if the data regarding the domain were 'reported and adequate', 'reported but inadequate' and 'not reported', respectively.

Data extraction

Data were extracted from each study without modifications and reported in 2×2 contingency tables. Two dichotomous qualitative variables were reported in the tables:

EH category ('S-EH' or 'C-EH');
progression to cancer ('no cancer' or 'cancer').

Data analysis

The impact of glandular complexity on the risk of cancer was assessed by calculating the relative risk (RR) for progression to cancer. Values were reported for each study and as pooled estimate on forest plots, with 95% confidence interval (CI). A p-value < 0.05 was considered significant.

Statistical heterogeneity among studies was quantified by using the inconsistency index I^2: heterogeneity was considered null for $I^2 = 0\%$, minimal for $I^2 < 25\%$, low for $I^2 < 50\%$, moderate for $I^2 < 75\%$ and high for $I^2 \geq 75\%$. The random effect model of DerSimonian and Laird was used only if $I^2 > 50\%$; otherwise, a fixed-effect model was adopted.

Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used for the analysis.

Risk of Bias across studies assessment

The risk of bias across studies was assessed by using a funnel plot, reporting the several studies on a plan based on RR values (on the x axis) and the standard error (on the y axis). The risk of publication bias was significant if the funnel plot was asymmetrical and if the studies with higher standard error (which indicate low study accuracy) showed higher RR.

RESULTS

Selection and characteristics of the studies

Eight retrospective studies with a total of 1066 EH without atypia were included (11–18). The whole process of study selection is reported in Fig. 1.

Seven studies were designed as retrospective cohorts and one as case-control. Endometrial sampling was performed by curettage in most studies;

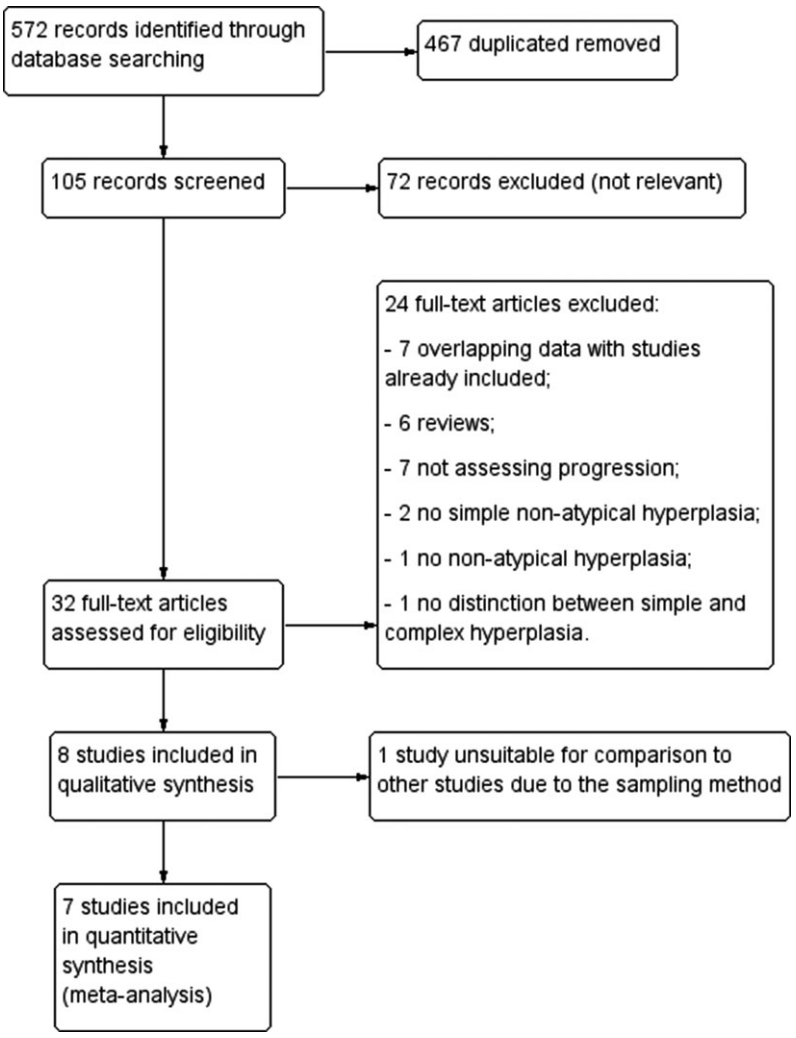

Fig. 1. Flow diagram of studies identified in the systematic review (Prisma template [Preferred Reporting Item for Systematic Reviews and Meta-Analyses]).

other methods included vacuum aspiration, Pipelle biopsy and hysteroscopic biopsy.

Characteristics of the included studies are reported in Table 1.

Risk of bias within studies assessment

For the 'patient selection' domain, one study was considered at high risk of bias due to its design (case-control with oversampling of A-EH (12)), which makes it unsuitable for comparison with other studies.

For the 'index diagnosis' domain, three studies were considered at unclear risk, because the index sampling method was not specified or not uniform.

For the 'reference diagnosis' domain, six studies were considered at unclear risk, because it was not stated whether all cancer diagnoses were confirmed on hysterectomy specimens.

For the 'flow and timing' domain, two studies were considered at unclear risk, since patients with a follow-up < 1 year were also included.

All remaining judgments for each domain were at 'low risk of bias'. Results of the risk of bias assessment are shown in Fig. 2.

Meta-analysis

Seven studies were included in the meta-analysis; the study at high risk of bias was excluded.

Table 1. Characteristics of the included studies. [C]: patient with coexistent cancer; [N]: patient with no coexistent cancer

Study	Country	Institute	Design	Period of enrollment	Total sample size	Sample of interest	Patients age (mean)	Sampling method	Classification adopted	Follow-up (mean)	Progression diagnosis
Kurman et al. (1985) (13)	USA	Armed Forces Institute of Pathology	Retrospective cohort	1940–1970	170	122	17–71	Curettage	WHO	1–27 years (13)	Variable
Baak et al.(1992) (14)	Nether-lands	University Hospital, De Boelelaan	Retrospective cohort	<1985	39	14	(53)[C] (40)[N]	Curettage	WHO, EIN	6–52 months (17)[C] (32 months)[N]	Hysterectomy
Orbo et al. (2000) (15)	Norway	University Hospital of Tromsø	Retrospective cohort	1980–1991	68	19	28–77 (48)	Curettage	WHO, EIN	3–39 months (7)[C] 2–21 years[N]	Hysterectomy
Baak et al. (2001) (16)	Nether-lands, Norway	Multicentre	Retrospective cohort	1988–1998	132	71	34–77 (58)[C] 20–93 (50)[N]	Curettage	WHO, EIN	1–10 years (not excluding earlier cancers)	n.r.
Baak et al. (2005) (11)	Europe, America	Multicentre	Retrospective cohort	22 years period (un-specified)	674	467	n.r.	Curettage, aspiration, Pipelle	WHO, EIN	13–120 months (48)[C] 13–216 months (68)[N]	n.r.
Hecht et al. (2005) (17)	Israel	Beth Israel Hospital	Retrospective cohort	1998–2000	97	63	n.r.	Biopsies, curettages	WHO, EIN	At least 1 year (not excluding earlier cancers)	Variable
Lacey et al. (2008) (12)	USA	Kaiser Permanente Northwest Department of Pathology	Case-control	1970–2002	379	170	n.r.	n.r.	WHO, EIN	At least 1 year (68 days) hysterectomized (3 years) others	n.r.
Steinbakk et al. (2011) (18)	Norway	Stavanger University Hospital	Retrospective cohort	1980–2004	152	140	21–88 (53)	Curettage	WHO, EIN	12–238 months (57)	n.r.
Total				1940–2004	1711	1066	–	–	–	–	–

WHO, World Health Organization; EIN, Endometrial Intraepithelial Neoplasia.

The risk for progression to cancer was significantly higher in C-EH than in S-EH ($p < 0.0001$), with an RR or 4.90 (96% CI: 2.21–10.86). Heterogeneity among studies was completely absent ($I^2 = 0\%$) (Fig. 3).

The funnel plot showed symmetric distribution of RR values, indicating that the risk of publication bias was not significant (Fig. 4).

DISCUSSION

Main findings and interpretations

Our study showed that, in the absence of cytologic atypia, the complexity of glandular architecture significantly increases the risk of progression of EH to cancer, with a risk increase of almost 5-fold.

The diagnosis of EH is a long-standing issue. Before the 1994 WHO classification, there was no univocal system for EH categorization. One of the most used systems had classified EH into 'cystic glandular' (increased gland-to-stroma ratio without significant crowding, cystically dilated glands), 'adenomatous' (closely packed glands with irregular profile) and 'atypical adenomatous' (with superimposed cytologic atypia) (4). The 1994 WHO classification, based on a large study by Kurman et al., had classified EH according to two crucial parameters: complexity of glandular architecture and cytologic atypia, defining four categories of EH: 'simple non-atypical', 'complex non-atypical', 'simple atypical' and 'complex atypical' (2, 13). The category of 'simple atypical EH' did not correspond to any previous category and was removed in the 2003 revision, returning to a triple classification into 'S-EH', 'C-EH' and 'A-EH' (4). Alongside WHO, an alternative classification system was developed, the Endometrial Intraepithelial Neoplasia (EIN) system. The EIN system arose from morphometric and molecular studies in the 1980s and 1990s, which showed that EH actually had a dual nature. Indeed, some EH are polyclonal, dysfunctional proliferation, while other ones are true precancerous lesions. The EIN system separates EH into 'benign EH' and 'EIN', based on the presence of three morphologic parameters: glandular crowding, lesion diameter > 1 mm and cytology different from adjacent endometrium. The EIN system has outlined that premalignant EH arise as a focal lesion, distinct from the background endometrium, while benign EH is diffuse (2, 3, 19). Given the scientific impact of EIN system, in 2014 the WHO had proposed a dual classification of EH into 'non-atypical' and 'atypical'. The 2014 classification reports 'A-EH' and 'EIN' as synonyms, adopting the same conceptual basis as the EIN system (1).

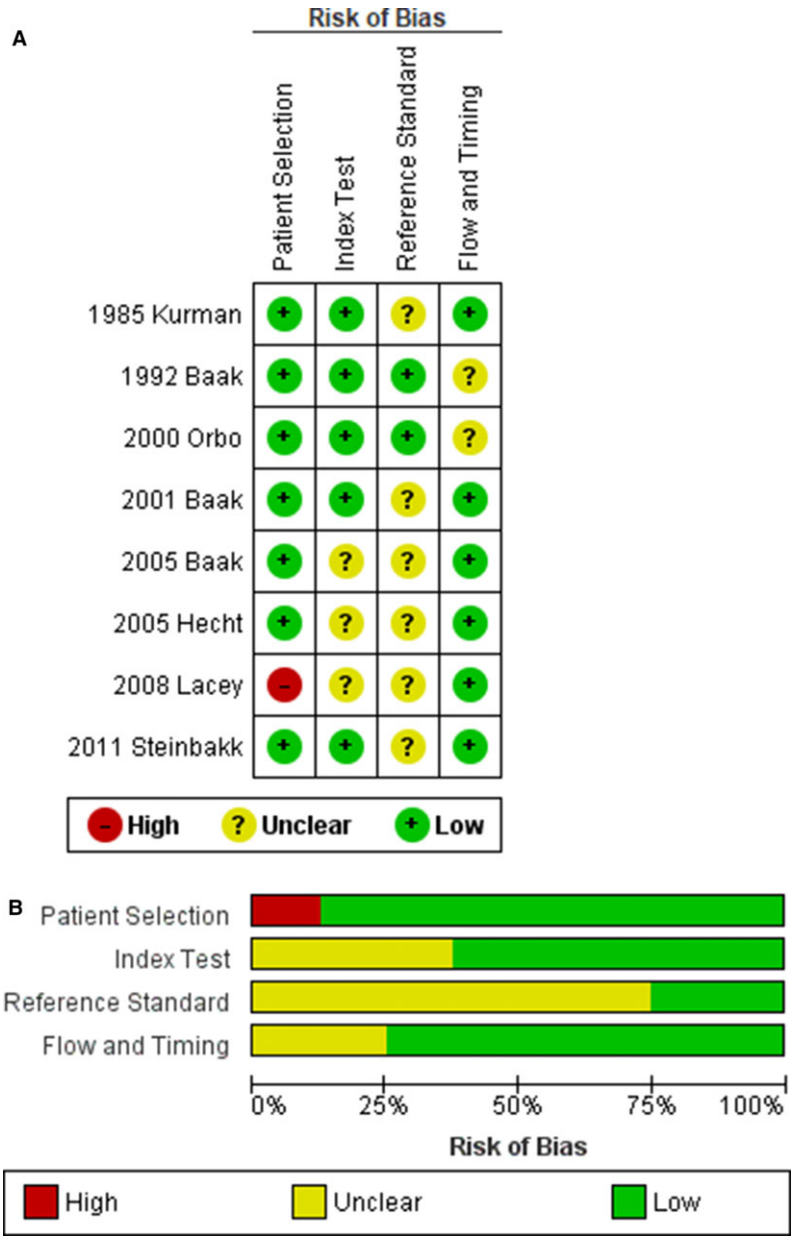

Fig. 2. (A) Assessment of risk of bias. Summary of risk of bias for each study; plus sign: low risk of bias; minus sign: high risk of bias; question mark: unclear risk of bias. (B) Risk of bias graph about each risk of bias item presented as percentages across all included studies.

However, the WHO 2014 terminology appears confounding, as it is unclear if the acronym 'EIN' (written in full as 'endometrioid intraepithelial neoplasia') actually refers to the EIN (endometrial intraepithelial neoplasia) system. In fact, the current WHO classification is not well integrated with EIN criteria, but it appears based on the only one parameter of cytologic atypia, which includes nuclear enlargement, pleomorphism, rounding, loss of polarity and nucleoli (19). On the other hand, the EIN system takes into account the presence of glandular crowding, which is a crucial feature in C-EH. Furthermore, the irregularity of glandular profile observed in C-EH has been a major parameter in morphometric analyses underlying the EIN system (3).

Although the EIN system has been reported to outperform the WHO system in the risk

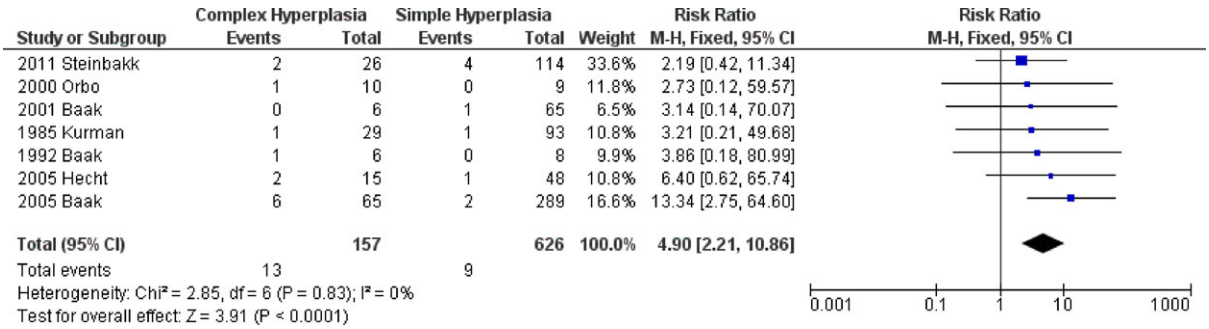

Fig. 3. Forest plot reporting relative risk values for the risk of coexistent cancer in complex hyperplasia without atypia vs simple hyperplasia without atypia, for each study and as pooled estimate, with 95% confidence interval.

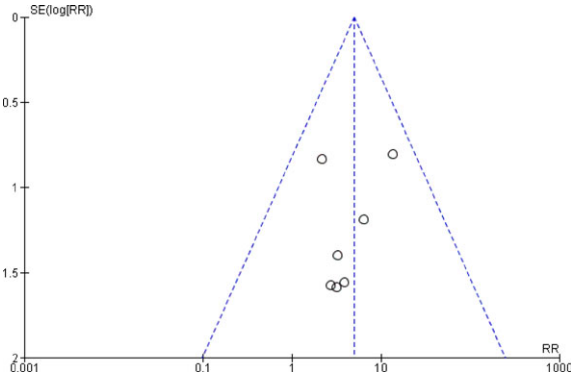

Fig. 4. Funnel plot for the assessment of the risk of bias across studies, reporting relative risk on the *x* axis and standard error (ER) on the *y* axis.

stratification of EH, most of these results regard the objective assessment of EIN criteria, based on a computerized morphometric assessment, which is not widely available (3, 11). On the other hand, the superiority of the 'subjective' EIN system over the WHO system is still the subject of debate (12).

In our previous studies, we investigated the expression of Bcl-2, PTEN and PAX2 – three molecules involved in endometrial carcinogenesis – in EH. We found that, for Bcl-2 and PAX2, an aberrant expression correlated with EIN criteria of premalignancy better than with the WHO criteria, while no significant difference was found for PTEN (20–22). Furthermore, in another study we found that the EIN system was more sensitive, but less specific than the WHO one for the risk of cancer coexistent with EH (19). In these studies, we postulated that a major cause of the difference between WHO and EIN system may lie in the 'complex non-atypical EH' category. Indeed, it has been shown that many C-EH meet EIN criteria of premalignancy. Cytologic features of EIN may be only slightly different from normal endometrium, in the absence of overt atypical features (nuclear rounding and enlargement, loss of polarization, presence of nucleoli). A delimited lesion > 1 mm, characterized by glandular crowding, with minimal cytologic difference from adjacent endometrium, in the absence of overt nuclear atypia, would fall in the benign category according to the WHO system, and in the premalignant category according to the EIN system. This would explain both the higher sensitivity and the lower specificity of EIN system compared to the WHO one.

All these observations suggest that many C-EH might be regarded as 'low-risk' premalignant lesion, i.e. they are monoclonal, harbor the typical genetic alteration of EC, but are in an early phase of carcinogenesis. Consistently, our current study showed a 4.9-fold increase in the risk of progression to cancer, which is lower than the risk increase related to atypical EH, but still significant.

In order not to miss these premalignant lesions, we have previously proposed an integration of the WHO system with the EIN system. Basically, we have suggested to use the EIN criteria to recognize premalignant EH, substratifying them based on the presence of overt cytologic atypia. According to such an approach, three EH categories would be identified: benign EH (polyclonal); EIN without overt atypia (premalignant, but with lower risk of cancer); EIN with overt atypia (premalignant, but with higher risk of cancer) (19).

In our experience, endometrial biopsies with cytologically ambiguous areas of crowded glands are common. In these patients, a diagnosis of A-EH/EIN may lead to hysterectomy, in particular if they do not wish to get pregnant or if they were already conservatively treated. On the other hand, a diagnosis of benign EH might lead to undertreatment with subsequent occult progression of the lesion. In these cases, a diagnosis of 'EIN without overt atypia', or low-risk premalignant lesion, may

indicate the need to treat and follow the patients, in the absence of the imminent risk of cancer. Furthermore, in women conservatively treated, the aggressiveness of treatment (e.g., oral progestins, intrauterine progestins, hysteroscopic resection plus progestins) and the timing of follow-up might be defined according to the presence of overt atypia, since molecular or immunohistochemical predictive markers have shown little value (23, 24). Finally, in women addressed to hysterectomy, the presence of overt atypia might direct the surgical priority.

Such an approach may lead to a more tailored management of women with EH.

Further studies are necessary to confirm the use of this combined classification in the common practice and all its possible clinical implications.

Strengths and limitations

To the best of our knowledge, this is the first meta-analysis assessing the impact of the complexity of EH glandular architecture on the risk of progression to cancer. Our analysis showed complete absence of heterogeneity among studies, and absence of publication bias, giving solidity to our results. Furthermore, our findings are consistent with the scientific evidence in this field, as widely discussed above.

Some limitations may affect our results. The duration of follow-up varies among studies. Some authors included patients with a follow-up < 1 year, creating a possible confusion between progression of EH to cancer and coexistence of cancer with EH. However, the presence of coexistent cancer might have a significance similar to the progression to cancer, as it still identifies EH at higher risk.

Progression rates might also vary based on the patient management (i.e., whether or not the patient was treated before hysterectomy; which type of progestin was administered; whether or not hysteroscopic resection was performed) (6, 7).

Furthermore, the low reproducibility of the diagnosis of EH and its morphologic parameters (architecture complexity, nuclear atypia) might be a major limitation, despite being intrinsic to the topic assessed (25).

CONCLUSION

The complexity of glandular architecture increases the risk of cancer in EH independently from the presence of overt cytologic atypia. Despite being considered benign by the current WHO classification, the category of 'complex non-atypical EH' includes many monoclonal lesions, which may be regarded as low-risk premalignant lesions. The EIN system might be useful not to miss these precancers, which may be referred to as 'EIN without overt atypia' or 'low-risk EIN'. Further studies are necessary to confirm the validity of such approach.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

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