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Review Article

Factors Associated with Malignancy in Hysteroscopically Resected Endometrial Polyps: A Systematic Review and Meta-Analysis

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ABSTRACT In this study, we aimed to estimate the frequency of premalignant and malignant lesions in endometrial polyps, and to evaluate associated clinical and demographic factors. A literature search was performed in major databases and the gray literature using the terms polyps OR endometrial polyp AND endometrial neoplasms OR endometrial cancer OR endometrial hyperplasia OR malignan*. Studies describing the frequency of premalignant and malignant lesions in endometrial polyps and any clinical or demographic factors associated with malignant lesions extracted using hysteroscopy were considered eligible. Independent investigators selected the studies and extracted the data. A meta-analysis was performed using a random-effects model and meta-regression. We identified 37 studies (comprising 21,057 patients) of endometrial polyps. The prevalence of premalignant and malignant lesions was 3.4% (95% confidence interval [CI], 2.8–4.1; I^2, 80.5%). Abnormal uterine bleeding (prevalence ratio [PR], 1.47; 95% CI, 1.27–1.69; I^2, 82.4%), menopausal status (PR, 1.67; 95% CI, 1.48–1.89; I^2, 78.4%), age >60 years (PR, 2.41; 95% CI, 1.84–3.16; I^2, 81.5%), diabetes mellitus (PR, 1.76; 95% CI, 1.43–2.16; I^2, 0.0%), systemic arterial hypertension (PR, 1.50; 95% CI, 1.20–1.88; I^2, 75.9%), obesity (PR, 1.41; 95% CI:1.13–1.76; I^2, 41.2%), and tamoxifen use (PR, 1.53; 95% CI, 1.06–2.21; I^2, 0.0%) were associated with endometrial polyp malignancy. However, breast cancer (PR, 0.83; 95% CI, 0.44–1.57; I^2, 0.0%), hormonal therapy (PR, 0.93; 95% CI, 0.67–1.30; I^2, 31.7%), parity (PR, 0.87; 95% CI, 0.39–1.96; I^2, 78.1%), and endometrial polyp size (PR, 1.05; 95% CI, 0.70–1.57; I^2, 44.7%) were not associated with malignancy of endometrial polyps. Three of every 100 women with clinically recognized polyps, a condition associated with specific clinical and demographic factors, will harbor premalignant or malignant lesions. Journal of Minimally Invasive Gynecology (2018) ■■, ■■–■■ © 2018 AAGL. All rights reserved.

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Endometrial polyps, prominent lesions occurring on the surface of the endometrium, affect 10% to 40% of women worldwide [1]. The prevalence of this condition varies depending on the diagnostic method used and the population considered [1–3]. Surgical hysteroscopy is considered the gold standard for surgical excision and further histopathological evaluation of this lesion [4].

Although endometrial polyps are usually benign, the risk of malignancy should not be overlooked. The American Association of Gynecologic Laparoscopists (AAGL) estimates that the prevalence of malignancy in endometrial polyps ranges between 0% and 12.9%, depending on the subgroup [4].

Studies have shown that some factors are linked to malignancy in endometrial polyps [5,6]. However, a wide search of the literature did not identify a meta-analysis that evaluated patients with endometrial polyps with regard to risk factors for endometrial cancer, such as obesity, parity, tamoxifen use, hormonal therapy use, and others. Some studies have suggested that hysteroscopy is appropriate for all patients with endometrial polyps, because it is not possible to identify malignancy in endometrial polyps without histopathological evaluation of the lesions [7–13]. Others have recommended against hysteroscopy as a routine technique [1,4,14–36].

Determining the factors associated with malignancy in endometrial polyps is important to help identify patients at

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increased risk of malignant endometrial lesions compared with the general population. Our present systematic review and meta-analysis aimed to estimate the frequency of premalignant and malignant lesions in endometrial polyps in patients who underwent surgical hysteroscopy, and to investigate associations between malignancy and clinical and demographic factors.

Methods

Protocol and Registration

This review was registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration no. CRD42015027913) and conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Eligibility Criteria, Information Sources, and Search Strategy

All studies describing the frequency of premalignant and malignant lesions in endometrial polyps and any clinical or demographic factors associated with these lesions were considered eligible. For inclusion in our meta-analysis, a study had to involve excision of endometrial polyps via surgical hysteroscopy. In addition, the histopathological analysis should have described the polyp as benign (i.e., endometrial polyps or polyps with either simple or complex hyperplasia without atypia), premalignant, or malignant (i.e., polyps with either simple or complex hyperplasia with atypia or endometrial cancer).

Studies were excluded that did not classify cases as benign and premalignant or malignant or that described only the population with the condition and did not include a nonaffected population as a control. The study design, sample size, publication date or status, language, and study site were not part of the exclusion criteria in this review.

The following databases were searched: MEDLINE (via PubMed), EMBASE, Scopus, LILACS, SciELO, Web of Science, Google Scholar, Database of Thesis and Dissertations of CAPES, and ClinicalTrials.gov. Furthermore, we searched the bibliographic references of relevant identified studies to select potentially eligible studies. Efforts were made to include all available studies, including contact with the authors as needed.

We developed the search strategy using MeSH terms for PubMed, EMTREE terms for EMBASE, and a combination of key words. The complete search strategy used on PubMed was ("polyps"[MeSH] OR "endometrial polyp" OR "endometrial polyps") AND ("Endometrial Neoplasms"[MeSH] OR "Endometrial Cancer" OR "Endometrial Hyperplasia"[MeSH] OR "malignan*" [tiab]). The same search was modified for each database. The literature search for potentially eligible studies was performed to identify articles published before March 2016 (Appendix S1).

Study Selection

After duplicates were removed, 2 independent researchers (L.P.S. and K.R.C.A.) experienced in systematic reviews screened the literature in 2 stages (title and abstract, followed by full text) using Covidence software, one of Cochrane's recommended tools for supporting authors in the preparation of systematic reviews [37]. A decision was made by consensus when the researchers disagreed. For papers for which a consensus could not be reached by the 2 authors, a third author helped determine acceptance.

Data Collection Process

Two researchers independently extracted the following data onto a standardized datasheet: study characteristics, sample size, prevalence, and clinical and demographic factors associated with malignancy in endometrial polyps. In cases where a consensus could not be reached by the 2 authors, the disagreements were resolved by discussion between the 2 reviewers or by a third reviewer. If details of the selected studies were unavailable, we contacted the corresponding authors.

Assessment of Risk of Bias

Study quality was evaluated by 2 independent researchers (L.P.S. and KRCA) using a tool described by Munn et al. [38] and Da Mata et al. [39]. Studies were considered of good quality whenever there were at least 7 "yes" answers, of medium quality when there were 4 to 6 "yes" answers, and of low quality with 0 to 3 "yes" answers. No study was initially excluded based on methodological quality.

Data Items

The prevalence of premalignant and malignant lesions in endometrial polyps and associated factors was estimated according to a measure of association, the prevalence ratio (PR) and its 95% confidence interval (CI). A meta-analysis was performed using the random-effects model with an inverse-variance method. The heterogeneity between studies and the inconsistency magnitude was evaluated using the χ^2 test, which yielded the I^2 statistic. Heterogeneity was considered high at I^2 >75%, moderate at I^2 of 25% to 75%, and low at I^2 <25%.

Risk of Bias

Publication bias was investigated via a visual inspection of funnel plots and the use of Begg's test. Bias was considered statistically significant at $p < .05$.

Additional Analyses

We performed a sensitivity analysis to identify possible causes of heterogeneity and to ascertain which studies might