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Review

The accuracy of endometrial sampling in women with postmenopausal bleeding: a systematic review and meta-analysis

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ABSTRACT

Postmenopausal bleeding (PMB) can be the first sign of endometrial cancer. In case of thickened endometrium, endometrial sampling is often used in these women. In this systematic review, we studied the accuracy of endometrial sampling for the diagnoses of endometrial cancer, atypical hyperplasia and endometrial disease (endometrial pathology, including benign polyps).

We systematically searched the literature for studies comparing the results of endometrial sampling in women with postmenopausal bleeding with two different reference standards: blind dilatation and curettage (D&C) and hysteroscopy with histology. We assessed the quality of the detected studies by the QUADAS-2 tool. For each included study, we calculated the fraction of women in whom endometrial sampling failed. Furthermore, we extracted numbers of cases of endometrial cancer, atypical hyperplasia and endometrial disease that were identified or missed by endometrial sampling.

We detected 12 studies reporting on 1029 women with postmenopausal bleeding: five studies with dilatation and curettage (D&C) and seven studies with hysteroscopy as a reference test. The weighted sensitivity of endometrial sampling with D&C as a reference for the diagnosis of endometrial cancer was 100% (range 100–100%) and 92% (71–100) for the diagnosis of atypical hyperplasia. Only one study reported sensitivity for endometrial disease, which was 76%. When hysteroscopy was used as a reference, weighted sensitivities of endometrial sampling were 90% (range 50–100), 82% (range 56–94) and 39% (21–69) for the diagnosis of endometrial cancer, atypical hyperplasia and endometrial disease, respectively. For all diagnosis studied and the reference test used, specificity was 98–100%. The weighted failure rate of endometrial sampling was 11% (range 1–53%), while insufficient samples were found in 31% (range 7–76%). In these women with insufficient or failed samples, an endometrial (pre) cancer was found in 7% (range 0–18%).

In women with postmenopausal bleeding, the sensitivity of endometrial sampling to detect endometrial cancer and especially atypical hyperplasia and endometrial disease, including endometrial polyps, is lower than previously thought. Therefore, further diagnostic work-up for focal pathology is warranted, after a benign result of endometrial sampling.

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Introduction

Postmenopausal bleeding (PMB) is one of the most frequent complaints with which women present in the outpatient gynecology clinic. As PMB might be the first sign of endometrial cancer, accurate diagnostic work up is necessary in these women. Despite many studies on the different diagnostic measures in women with PMB, there is no consensus on the best diagnostic pathway [1–4].

In many guidelines the measurement of endometrial thickness by transvaginal sonography (TVS) is used as a first step in the diagnostic pathway to distinguish women with a low and a high risk of having endometrial cancer. Clark et al. found that a strategy with TVS as the initial test with a cut-off of 4 mm followed by endometrial sampling was the most cost-effective [5]. In situations where ultrasound is not directly available, endometrial sampling can be used as the first step [6].

The meta-analysis by Dijkhuizen et al. was the first meta-analysis on the diagnostic accuracy of endometrial sampling in women with postmenopausal bleeding [7]. Several years after that, two other meta-analyses were published [8,9]. These meta-analyses found that sensitivity, which is crucial to rule out endometrial cancer, was around 99%. However, in these studies (blind) dilatation and curettage (D&C) had been used as reference standard. Nowadays, D&C is almost completely replaced by hysteroscopy as a reference standard [10]. Also, only a small proportion of women in these meta-analyses was postmenopausal.

In view of this, we decided to conduct a systematic review and meta-analysis to study the diagnostic accuracy of endometrial sampling in women with PMB regarding the diagnoses of endometrial cancer and atypical hyperplasia compared to two different reference standards: blind D&C and the current reference standard: hysteroscopy with histology or hysterectomy [10].

Methods

Identification of studies

In April 2015, we performed a computerized search in MEDLINE, EMBASE and Science Direct® to identify all studies on the diagnostic accuracy of endometrial sampling published between January 1965 and March 2015. The search was limited to studies in humans; language restrictions were not applied. We used all known synonyms for the following keywords: postmenopausal bleeding AND endometrial sampling. We included observational studies on the evaluation of the diagnostic accuracy of endometrial sampling in women with PMB. References cited in the selected articles were checked for further relevant articles not identified by the electronic searches. The search strategy can be found in the Appendix.

Selection criteria

This review focused on diagnostic studies in which the histology results of endometrial sampling were compared with the results of a reference standard. The articles had to study women with postmenopausal uterine bleeding, the diagnostic test of interest was endometrial sampling (histology), the reference standard had to be endometrial histological findings from (blind) D&C, diagnostic hysteroscopy with histology by targeted biopsy or D&C or hysterectomy.

Identified articles were merged into a common file, duplicates were deleted, and results were divided between two reviewers (NvH and MMP) who independently examined the assigned articles and classified each as "exclude", "include", or "unsure." Initial screening began with a title screen. Subsequently, abstracts were retrieved and screened to determine eligibility. Finally, full text articles were retrieved and screened for inclusion. A third reviewer (MB) settled discrepancies. For articles, which included both pre- and postmenopausal women, but did not report separately on the postmenopausal group, we sent an email to the corresponding author to ask for the data on postmenopausal women. For articles which were published before 1997 and therefor no of the corresponding author was mentioned, we searched the internet (Google, PubMed) for an to contact the corresponding author. We calculated the agreement on the selection of studies between the reviewers.

Quality assessment

Two reviewers (NvH and MMP) independently assessed the methodological quality of each selected paper using the QUADAS-2 tool for diagnostic studies, modified to conform to this review [11]. Disagreements were resolved via consensus and if necessary via consensus of a third reviewer (MB).

We decided a priori the criteria of each study for low risk of bias in each of the four main domains of the Quadas-2 tool: patient selection, index test, reference standard, and flow and timing [11]. For patient selection, the in- and exclusion criteria had to be clearly stated, and the patient sample had to be consecutive. For the index test, the independent assessment of the pathologist for endometrial