Management of endometrial abnormalities in postmenopausal women, an individualized approach
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General introduction

Partially adapted from:


Postmenopausal bleeding (PMB), defined as blood loss occurring at least 12 months after menopause, is a common complaint in general gynecological practice. The prevalence of PMB is approximately 10% immediately after menopause. Postmenopausal bleeding (PMB) signals endometrial carcinoma in around 10% of cases or less serious conditions, such as benign endometrial polyps, in a further 20–40%. Endometrial carcinoma is the most common gynecologic malignancy and 95% of women with endometrial carcinoma present with PMB. Unlike ovarian cancer, endometrial cancer often presents at an early stage, when there is a possibility of curative treatment by hysterectomy (and bilateral salpingo-oophorectomy); therefore early, accurate and timely diagnosis is important and any PMB needs further investigation. There are five different diagnostic tests available to investigate women with PMB: transvaginal sonographic (TVS) measurement of endometrial thickness, saline infused sonography (SIS), outpatient endometrial biopsy, hysteroscopy and dilatation and curettage (D&C). D&C was traditionally the method of choice for investigating women with PMB. In approximately 60% of the D&C procedures however, less than half of the uterine cavity is evaluated by the curettage. Another drawback of D&C is that this procedure is performed under general anesthesia in an inpatient setting. Endometrial biopsy and hysteroscopy have now almost completely replaced D&C.

Transvaginal sonography
The main goal of TVS is to exclude endometrial cancer. There are four meta-analyses published on this subject. Almost every guideline refers to the meta-analysis performed by Smith-Bindman et al. in 1998. It used traditional statistical methods to combine the data from 35 published studies regarding the use of TVS in the evaluation of women with PMB. Using the reported data from each study, 2 × 2 tables were constructed of endometrial thickness measured by TVS (above or below a threshold) against the presence or absence of endometrial carcinoma. With a cut-off value of 5 mm, the sensitivity for detecting endometrial carcinoma was 96%, and the specificity 61%. This combination of sensitivity and specificity reduces a pre-test probability of 10% for endometrial cancer to a post-test probability (for a negative test) of 1%. Thus, based on the post-test probability of 1%, conservative management is recommended to women with an endometrial thickness of ≤ 5 mm. The three other meta-analyses reached different conclusions.

Tabor et al. conducted a meta-analysis of nine studies. They included studies only if the corresponding author was able to supply original data. For each included study, the median endometrial thickness per center was calculated and multiples of the median were used to pool data. They chose not to use a cut-off value, because there were statistically significant differences in endometrial thickness between centers, which may reflect differences in the populations studied or in the method of measuring endometrial thickness by TVS. In this
study, a sensitivity of 96% and a specificity of 50% were found. These values give a post-test probability for a negative test of about 1% with a pre-test probability of carcinoma of 10%. These results are comparable to those of Smith-Bindman et al., but the authors disagreed on the interpretation of the results. The conclusion of Tabor et al. was that a 4% false-negative rate is not acceptable and therefore the use of TVS in the evaluation of PMB is not recommended prior to invasive testing.

Gupta et al. performed a systematic quantitative review in which they focused on study quality assessment. None of the nine studies that used a cut-off for endometrial thickness of ≤ 4 mm were of good quality. Only four studies (out of 15) used a ≤ 5 mm cut-off, but these employed the best quality criteria. Pooling of the results of these four studies resulted in a negative likelihood ratio of 0.16. This likelihood ratio implies that a patient with a negative test result (endometrial thickness ≤ 5 mm) and pre-test probability of 10% would have a post-test probability of 2.5%. Their conclusion was that TVS can be used to rule out endometrial hyperplasia or carcinoma using an endometrial thickness cut-off of ≤ 5 mm.

With respect to meta-analysis of randomized trials, individual patient data are considered to be superior to meta-analysis of the literature. The use of individual patient data instead of published summary data gives less optimistic but more accurate conclusions. In diagnostic reviews the same might apply. Timmermans et al. tried to overcome this limitation using a meta-analytic approach in which individual patient data from a series of original studies were combined. This study showed that in previous studies and meta-analyses, the diagnostic accuracy of TVS had been overestimated. Timmermans et al. found a lower diagnostic accuracy for TVS than was reported previously: a sensitivity of 95% and a specificity of 47% at a cut-off of ≤ 4 mm, giving a post-test probability for a negative test of 1.2%. At a cut-off of ≤ 3 mm, they found a sensitivity of 98% and a specificity of 35%, giving a likelihood ratio for a negative test result of 0.06. Thus, a cut-off level of ≤ 3 mm reduced a pre-test probability of 10% to a 0.7% post-test probability. The conclusion of this article was that the use of TVS measurement of endometrial thickness remains justified, but with a recommended cut-off level of ≤ 3 mm.

Invasive endometrial assessment methods

Endometrial biopsy

Dijkhuizen et al. performed a meta-analysis comparing different minimally invasive endometrial biopsy devices. In women with PMB, endometrial sampling with both the Pipelle device (Pipelle de Cornier, Paris, France) and the Vabra device (Berkeley Medevices, Inc., Richmond, CA, USA) are very sensitive techniques for the detection of endometrial carcinoma, with detection rates of 99.6% and 97.1% respectively. However, in a substantial number of cases outpatient endometrial sampling fails because of technical problems (12-23%) or because of an insufficient amount of tissue for a histopathological diagnosis.
In 6% of these failures, women are subsequently diagnosed with both malignant and premalignant disorders of the endometrial tissue and cannot be reassured without further testing.\textsuperscript{10}

**Hysteroscopy**

Compared with other methods, hysteroscopy offers the possibility of visualizing macroscopic or focal abnormalities and taking directed biopsies.\textsuperscript{15, 16} With the development of smaller diameter hysteroscopic systems and the introduction of a “vaginoscopic” approach to hysteroscopy (without the use of a speculum or tenaculum), patient acceptance has improved considerably and hysteroscopy nowadays can be performed in an outpatient setting without the use of anaesthesia.\textsuperscript{17-19} Clark et al.\textsuperscript{20} performed a systematic quantitative review in which they focussed on the diagnostic accuracy of hysteroscopy in diagnosing endometrial cancer or hyperplasia. Postmenopausal women represented 29% of the populations studied. Only two studies concerning postmenopausal women were rated as high quality. Pooled data from these studies showed a post-test probability of a positive test of 71.8% (95% CI 67.0–76.6%). Sensitivity and specificity were not separately described for pre- and postmenopausal women, but the overall sensitivity and specificity were 86.4% and 99.2% respectively. The authors concluded that when the uterine cavity is adequately visualized, hysteroscopy is highly accurate and clinically useful in the diagnosis of endometrial cancer. However, its high accuracy relates to diagnosing cancer rather than its exclusion.

Another systematic review and meta-analysis of diagnostic hysteroscopy was performed by van Dongen et al.\textsuperscript{21} This article focused on studies on the use of hysteroscopy in the diagnosis of intrauterine abnormalities rather than endometrial cancer per se, because Clark et al. had already shown in their meta-analysis that diagnostic hysteroscopy is accurate in the diagnosis of endometrial cancer.\textsuperscript{20} In this review five studies of postmenopausal women with homogeneous data were included. The pooled sensitivity and specificity in the assessment of uterine cavity abnormalities were 96% (95% CI 93–99%) and 90% (95% CI 83–95%) respectively. With a pre-test probability of uterine cavity abnormalities of 61.0% (the prevalence in this group), they found a post-test probability for a positive test of 93% (95% CI 88–95%). The conclusion was that this meta-analysis gives strong evidence that diagnostic hysteroscopy is accurate in the diagnosis of intrauterine abnormalities.

**International guidelines**

The published national and international guidelines describe different diagnostic pathways in the diagnostic work-up of women with postmenopausal bleeding.\textsuperscript{7, 22-25} All guidelines advise referral to a gynecologist for examination, cervical cytology and TVS or endometrial biopsy. In all guidelines except for the United States (US) guideline, the first step is TVS, based on the high sensitivity and non-invasive character of the procedure. Different
guidelines use different cut-off values of endometrial thickness, varying from 3 mm to 5 mm. These cut-off points are mostly based on the meta-analysis by Smith-Bindman, but also on Swedish literature, and the review by Gupta et al. The most important issue is what probability of endometrial carcinoma is deemed acceptable after a negative test. The US guideline recommends either TVS or endometrial biopsy. The European guidelines advice endometrial sampling only when the endometrial thickness is above the cut-off value, possibly together with a SIS to distinguish between diffuse and focal pathology. Where the endometrium is thin, the guidelines recommend conservative management. Only the Scottish guideline recommends further investigation if the clinician, the patient or both are not reassured. The exact sequence of investigation will depend upon clinical judgment, local resources, local expertise and patient preference.

**Prediction models for endometrial carcinoma in women with postmenopausal bleeding**

In women with PMB there is considerable variability in endometrial thickness and the likelihood of endometrial carcinoma. Individual patient characteristics, including age, time since menopause, obesity, hypertension, diabetes mellitus and reproductive factors, are associated with a higher risk of endometrial carcinoma. While the probability of PMB decreases with increasing age, the probability of endometrial cancer in women with PMB increases significantly with increasing age. The probability rises from 1% in women younger than 50 years of age to 24% in women older than 80 years.

In clinical practice, tests are commonly combined in diagnostic sequences and disease probabilities are usually estimated in a hierarchical manner: first combining information from history and examination, followed by additional information obtained from diagnostic tests. The post-test probability is not only dependent on test characteristics, but also on the pretest probability, which is altered by patient characteristics. However, current diagnostic policy in women with PMB is not based on these patient-specific risk factors, but only on one fixed cut-off point for endometrial thickness.

Several articles have studied this subject and developed models to estimate the individual chance of endometrial carcinoma in women presenting with PMB. For a successful implementation, a prediction model should be validated externally in an independent population. None of the prediction models developed are externally validated.

**Diagnostic strategies**

In Figure 1, a flowchart with possible diagnostic pathways is presented. Two areas in this flowchart require further research: (1) Modeling to calculate the individual probability of endometrial cancer based on patient characteristics and the implementation of such a model in daily practice and (2) the diagnostic approach to benign endometrial abnormalities after a malignancy has been ruled out.
Asymptomatic postmenopausal women

In contrast with the guidelines on the management of women with PMB, clinicians are faced with uncertainty when endometrial thickness is measured for asymptomatic postmenopausal women. Symptom free women sometimes undergo transvaginal ultrasound for other indications than postmenopausal bleeding such as prolapse or abdominal complaints. Inevitably, the endometrium is visualised and a thickened endometrium may then be observed. It is not known how to manage such patients in whom a thick endometrium is observed incidentally.

AIMS OF THE THESIS

1. To evaluate different diagnostic strategies for women with postmenopausal bleeding including strategies based on individual probabilities.
2. To study the value of endometrial thickness measurement in asymptomatic postmenopausal women.
OUTLINE OF THE THESIS

There are several articles on the development of prediction models to estimate the individual chance for endometrial cancer in women presenting with PMB. Chapter 2 describes a review to provide an overview of the existing prediction models for endometrial carcinoma in women with PMB.

Chapter 3 describes a decision analytic model to investigate the cost-effectiveness of three diagnostic strategies based on the individual probabilities of women presenting with PMB.

In Chapter 4 the results of an external validation study of two previously developed models on women with PMB are presented.

A study on which patient and doctor related factors contribute to the failure of outpatient endometrial biopsies and a multivariable prediction model on the failure of outpatient endometrial biopsies are presented in Chapter 5.

In Chapter 6 an analysis to investigate whether the multivariable prediction model described in chapter 5 could reduce the costs of diagnostic testing in women with PMB through a cost-minimization analysis is described.

In Chapter 7 the results of a study to determine whether structured assessment of endometrial biopsy specimens with strict criteria decreases the amount of inconclusive samples are presented.

Chapter 8 describes the results of a systematic review on the endometrial thickness, the prevalence of endometrial malignancy and the accuracy of endometrial thickness measurement in asymptomatic postmenopausal women.
REFERENCES

13. Stewart LA, Parmar MK. Meta-analysis of the literature or of individual patient data: is there a difference? Lancet 1993;341(8842):418-422.


