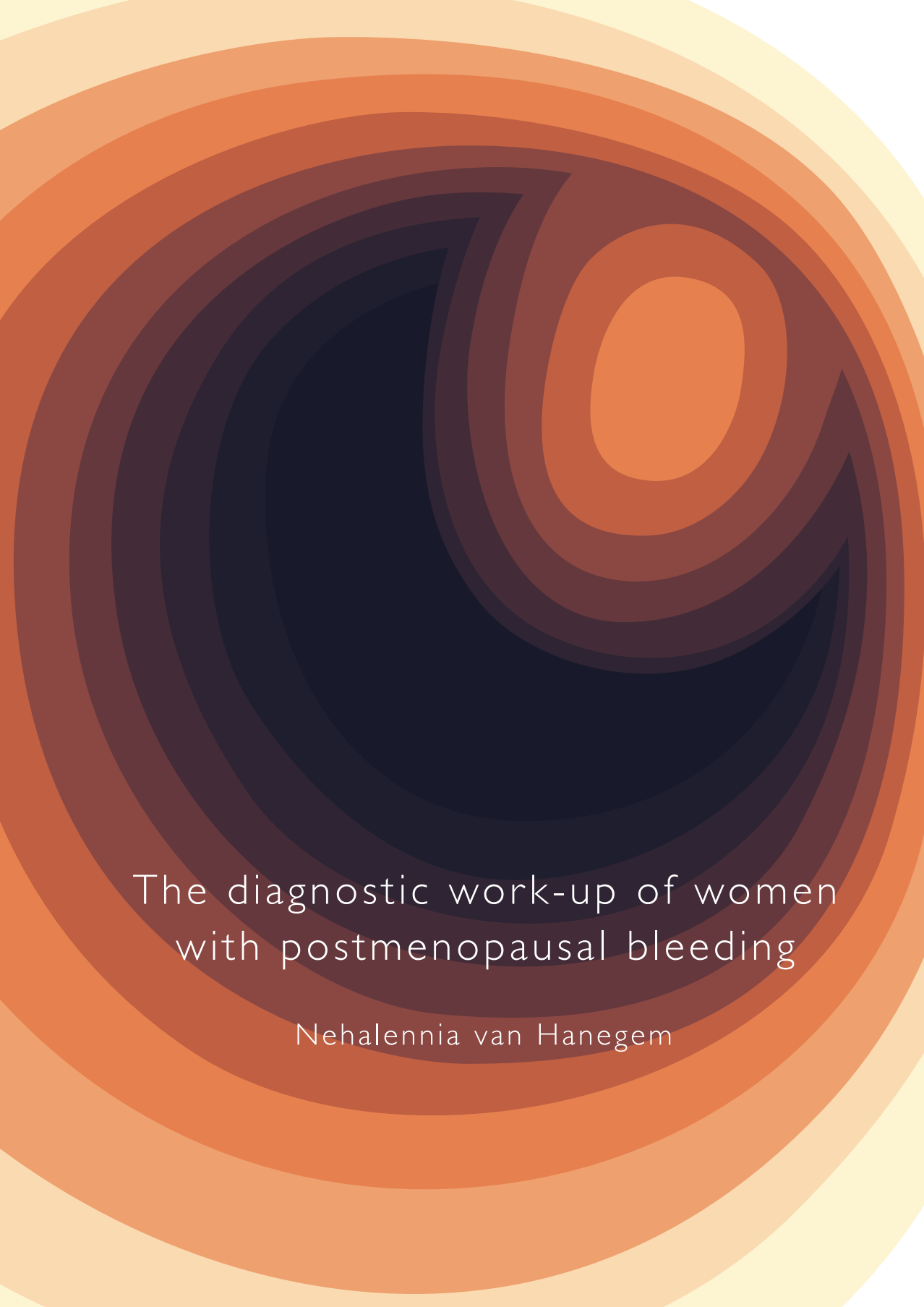

The diagnostic work-up of women with postmenopausal bleeding

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Contents

Chapter 1

General introduction

Background and problem

Endometrial cancer is defined as cancer from the lining or inside of the uterus (endometrium), and is the most common gynaecological cancer in industrialised countries. Endometrial cancer is linked to a higher age and obesity.[1-3] Worldwide, people are getting older and the incidence of overweight and obesity is rising.[4,5] The increase in both life expectancy and body weight increases people's risk of certain diseases. The incidence of endometrial cancer and precancer (atypical hyperplasia) is therefore expected to rise even further in the coming decades.[6]

The expected increase of women with endometrial cancer makes it all the more relevant to focus on ways to diagnose and treat the disease. If endometrial cancer is found at an early stage, curative treatment by removing the uterus and ovaries is still possible. Endometrial cancer can manifest diffuse in the endometrium or focal, inside an endometrial polyp. A common sign of endometrial cancer is vaginal bleeding, which makes its detection easier. For 95% of women with endometrial cancer, the disease presents in an early stage with postmenopausal bleeding (PMB), vaginal bleeding that occurs after a period of 12 months without menstruations at the menopausal age. To exclude endometrial cancer, it is therefore considered important to investigate all women who present with PMB.[7]

Yet, although women with PMB have an approximately 10% risk of having endometrial cancer, the majority of these women, instead of having endometrial cancer, have benign endometrial pathology or atrophy. Frequent findings in women with PMB are endometrial polyps, with a prevalence of about 20% in the general population of women with PMB, and of about 40% in women with both PMB and a thickened endometrium.[8,9] Endometrial polyps are believed to be responsible for recurrent PMB[10,11], although sparse evidence is available on this. As a consequence, the removal of endometrial polyps is a subject of debate and research. Current guidelines on PMB leave room for individual doctors and patients to choose between expectant management or further diagnostics to diagnose and remove endometrial polyps.[7,12,13]

Diagnostic work-up of women with PMB thus focuses on *both* the exclusion of endometrial cancer and on the (possible) diagnosis and treatment of endometrial polyps. Despite the many studies investigating this, there is no consensus on the best diagnostic pathway. The diagnostic steps vary in different guidelines, depending on the structure of patient flow in different settings and healthcare systems, as well as the availability of specific procedures, for example, ultrasound, endometrial sampling

(a biopsy of the lining of the uterus, which is performed in an outpatient setting), saline infusion sonography (SIS, an ultrasound in which water or gel used to better visualise the inside of the uterus), out- or inpatient hysteroscopy (inspection of the inside of the uterus with a small camera). As a result, it is unclear whether extensive diagnostic work-up has to be performed in all women presenting with PMB to rule out both endometrial cancer and endometrial polyps. Maybe it is enough to select women with a high risk of endometrial cancer for further diagnostics and reassure the ones with a low risk. Furthermore, it is unclear if we can save patients with benign endometrial sampling from (unnecessary) invasive procedures, and whether such a strategy would be cost-effective.

Research objectives, questions and general approach

In order to address these gaps in the available literature, this thesis studies two aspects of diagnostic work-up of women with PMB. The first is the selection of women with a high or low risk of endometrial cancer. This selection can be done by selecting women based on their patient characteristics, using a prediction model or by selecting women based on the result of endometrial sampling. The second aspect is the diagnosis and treatment of (benign) endometrial polyps. More precisely, the thesis aims to answer six research questions:

1. What is known in the literature about the diagnostic work-up of women with PMB?
2. Which prediction models on the chance of endometrial cancer in women with PMB are available in the literature and which model shows the best performance?
3. Is a prediction model based on patient characteristics useful in daily practice to differentiate between women with a high or a low risk of endometrial cancer?
4. Is the diagnostic work-up for and the removal of benign endometrial polyps effective in women with PMB to prevent recurrent bleeding?
5. Is the diagnostic work-up for and the removal of benign endometrial polyps cost-effective in women with PMB?
6. Is the diagnostic accuracy of outpatient endometrial sampling as high as we thought based on previous literature?

Answering these questions in conjunction will help to assemble the most efficient diagnostic work-up of women with PMB, with the aim to miss as few diagnoses as possible of endometrial cancer and to perform as few (unnecessary) invasive procedures as possible. What follows is an elaboration of the specific research questions and the research conducted to answer them.

1. What is known in the literature about the diagnostic work-up of women with postmenopausal bleeding?

In the Netherlands, a general practitioner will refer a woman with PMB to a gynaecologist to exclude the presence of endometrial cancer. In the past, the principal method of diagnostic work-up of women with PMB was dilation and curettage (D&C), performed under general anaesthesia. This procedure was invasive and not very cost-effective. About three decades ago, the measurement of the endometrial thickness by transvaginal ultrasound (TVS) was introduced as a more patient-friendly way to distinguish between women with a low or high risk of having endometrial cancer.[14,15] Not all women needed to undergo a D&C anymore. We know now that D&C misses around 50-85% of focal intracavitary pathology and therefore is not accurate enough in the diagnostic work-up of women with PMB.[8] Today, D&C is almost completely replaced by outpatient endometrial sampling and hysteroscopy. However, there is still no consensus in (inter) national guidelines on the most accurate and efficient diagnostic pathway. To give an overview of different diagnostic tools and the different sequences in the use of these tools, we first review the existing literature on diagnostic work-up of women with PMB.

2. Which prediction models on the chance of endometrial cancer in women with PMB are available in literature and which model shows the best performance?

In women with PMB there is considerable variance in endometrial thickness and the likelihood of having endometrial cancer. A meta-analysis done by Smith-Bindman et al showed a mean endometrial thickness of 4 mm for women with normal histological findings, 10 mm for women with endometrial polyps, 14 mm for women with hyperplasia, and 20 mm for women with endometrial cancer.[16] Because of this variance, it would be useful to identify women with a high risk of having endometrial cancer based not only on an endometrial thickness of more than four millimetres,

but also on their patient characteristics. Age appears to be an important risk factor, but also other individual patient characteristics are associated with a higher risk of endometrial cancer, including obesity, time since menopause, hypertension, diabetes mellitus and nulliparity.[2,17-22] On the basis of existing research into the prevalence of these risk factors, prediction models to estimate the individual chance of having endometrial cancer have been developed. In this thesis, we systematically review the literature to map the different prediction models available on this subject. Additionally, we study their performance in internal validation to identify the model with the best performance to pinpoint women with a high risk of having endometrial cancer.

3. Is a prediction model based on patient characteristics useful in daily practice to differentiate between women with a high or a low risk of endometrial cancer?

To answer this question, we will externally validate a mathematical model based on patient characteristics with or without the combination of the measurement of the endometrial thickness. Such validation is necessary before a prediction model can be implemented into clinical practice.[23] The development of a prediction model can be divided into three phases: model development, internal and external model validation, and impact analysis. In internally validated models, the performance of the model is tested in the same data set in which the model was developed, or in a group of subsequent patients within the same centre. In external validation, the goal is to demonstrate generalizability and reproducibility in patients different from the patients used for derivation of the original model. Therefore, the prediction model is evaluated on new data collected from an appropriate patient population in a different centre.[24] To answer the above question, we externally validate a model based on patient characteristics showing good performance in internal validation. We will validate this model in two separate databases with women with PMB: one Dutch database and one Swedish database. External validation of this model is the first step towards implementing the model in clinical practice.

4. Is the diagnostic work-up for and the removal of benign endometrial polyps effective in women with PMB to reduce recurrent bleeding?

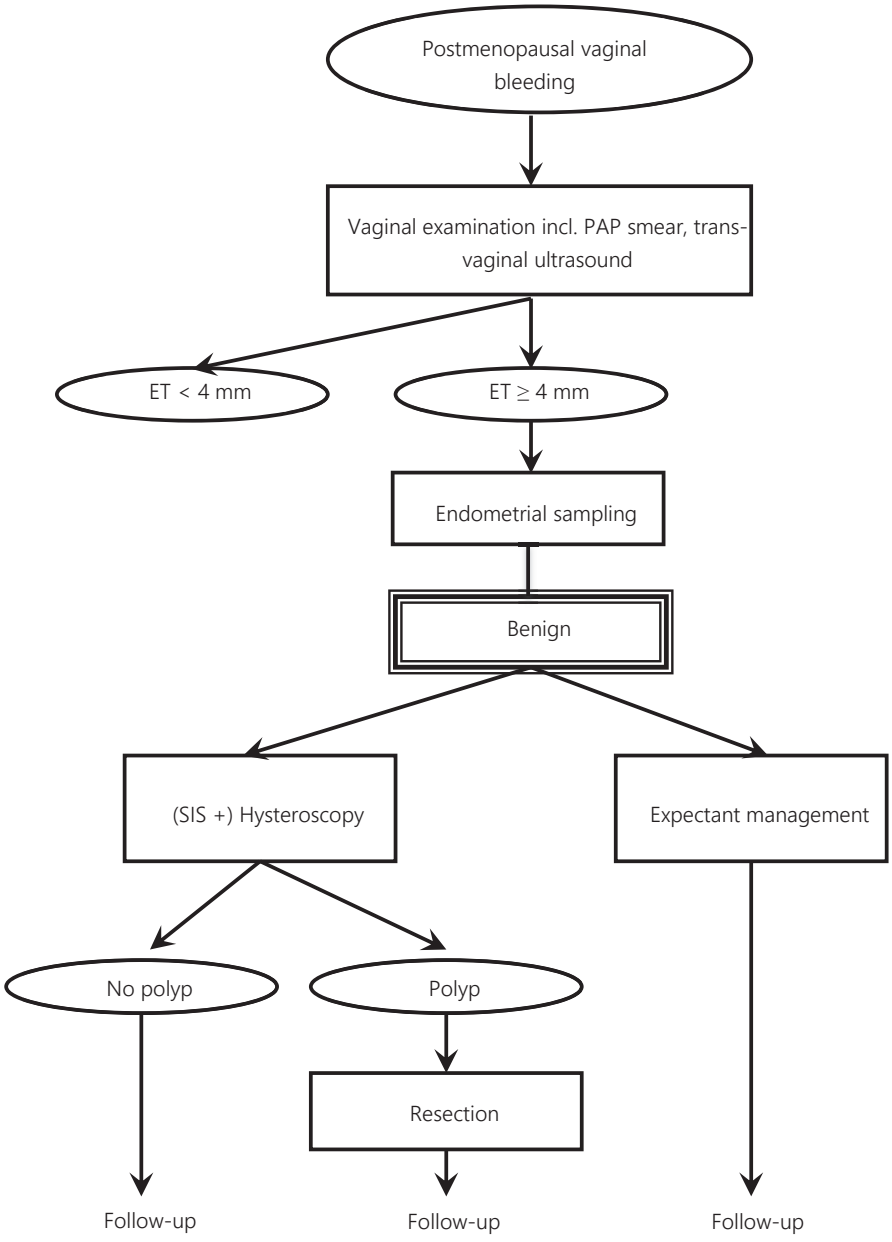
Although hysteroscopic polypectomy is one of the most frequently performed interventions in daily gynaecologic practice, only sparse evidence is available on

its effectiveness. In premenopausal women only one randomised trial has been done, which shows only a subjective decrease of the amount of bleeding after polypectomy was performed.[25] No randomised trials are available on the effectiveness of hysteroscopic polypectomy in women with PMB. The only cohort study, which researched the chance of recurrent bleeding in women with an endometrium of more than four millimetres (and therefore a higher chance of having a polyp), shows no difference in the number of women presenting with recurrent bleeding, regardless if these women underwent expectant management, a diagnostic hysteroscopy or hysteroscopic polypectomy.[26]

In an attempt to answer the question if polypectomy in women with PMB is effective to prevent recurrent bleeding, Timmermans et al conducted a randomised trial.[27] In this trial women with PMB and an endometrial polyp, diagnosed with hysteroscopy, were randomised between expectant management and polypectomy. Unfortunately, this study was stopped after 26 months because of lack of recruitment. A large majority of patients did not give informed consent once the polyp was diagnosed and also the doctors did not want to participate in the study once a polyp was diagnosed with hysteroscopy. To answer the above question, Timmermans et al suggested a different study-design. This study design can be found in Figure 1.

The design presented in Figure 1 addresses the effectiveness of diagnostic hysteroscopy and possible subsequent polypectomy in patients with PMB, rather than the effectiveness of polypectomy itself. The most important difference compared to the previous protocol is that women do not have to decide on polypectomy when the polyp is already diagnosed. Instead, the decision for further diagnostic work-up and for participation in this study is made after endometrial sampling shows a benign result. In this thesis, we describe the randomised trial performed according to the protocol suggested by Timmermans and colleagues.

Figure 1. Flowchart of study design (Figure extracted from Timmermans et al. BJOG 2009)



5. Is the diagnostic work-up for and the removal of benign endometrial polyps cost-effective in women with PMB?

In addition to clinical effectiveness of a treatment, costs of this treatment are also an important issue to consider, especially in times when significant financial cuts in healthcare are taking place. Alongside the above-described randomised trial on the diagnosis and treatment of endometrial polyps, we will perform an economic evaluation. In this study, we will perform a cost-effectiveness analysis in which we compare direct health care costs for the two groups in the randomised trial: hysteroscopy versus expectant management. Because we also perform an SIS in all patients in the hysteroscopy group, we are able to compare costs for a strategy in which SIS is used to select patients with a polyp for hysteroscopic polypectomy. Furthermore, we calculate the cost-effectiveness of (SIS and) hysteroscopy performed to diagnose women with endometrial (pre) cancer in a polyp.

6. Is the diagnostic accuracy of outpatient endometrial sampling as high as we thought based on previous literature?

Besides the reduction of recurrent bleeding, another reason to remove an endometrial polyp could be the underlying risk of endometrial (pre) cancer in the polyp. Literature does not clarify exactly how high this risk is. A systematic review on the risk of cancer in endometrial polyps describes a risk of 4.47% in women with PMB.[28] This could be an argument to remove all endometrial polyps in women with PMB. However, until now, (inter) national guidelines do not give a strict advice on this. Again, the guidelines leave room to the individual woman and doctor to choose for expectant management if the endometrium is more than four millimetres and endometrial sampling shows a benign result. From current literature, we can conclude that a benign result of endometrial sampling is reliable in these cases. In three meta-analyses, the sensitivity (a statistical measure, which gives the percentage of sick people who are correctly identified by the test as having the condition) of endometrial sampling has been tested.[29-31] All three articles include both pre- and postmenopausal women. The diagnostic accuracy of endometrial sampling in the small group of postmenopausal women is high, with a sensitivity of 97.0-99.6%. The most used device for endometrial sampling in the Netherlands is the Pipelle® and the post-test probability of endometrial cancer after a benign result of specifically

the Pipelle is only 0.8%.[30] However, this high sensitivity and low post-test probability are based on old studies, which use D&C as reference standard. In recent years, diagnostic hysteroscopy is considered to be the golden standard, which is more reliable in diagnosing focal endometrial pathology.[32] As a result, it is not known if the diagnostic accuracy of endometrial sampling in women with PMB is as high as the literature claims. Maybe, focal (pre) cancers are missed in the current diagnostic work-up. To study this subject, we will perform a meta-analysis on the diagnostic performance of endometrial sampling in women with PMB, with D&C compared to hysteroscopy as a reference standard.

Outline of the thesis

This thesis is structured into nine chapters, outlined below:

- **Chapter 2** presents the results of a systematic review, which provides an overview of the different diagnostic tools that are used for women with PMB.

- For clinical practice it would be useful to be able to stratify women with PMB into low versus high risk of having endometrial cancer based on patient characteristics. **Chapter 3** shows the results of a systematic review of the literature on existing prediction models. The most useful model in daily practice is identified by studying results of internal validation of these models.

- To implement a prediction model in clinical practice, external validation is essential. **Chapter 4** presents an external validation of a prediction model, which uses patient characteristics and ultrasound findings with a good performance in internal validation.

- In current guidelines, no consensus exists on further diagnostic work-up for and treatment of benign endometrial polyps. In **chapter 5** results are presented of a randomised controlled trial (RCT) on the diagnostic work-up of women with PMB, a thickened endometrium and a benign result of endometrial sampling to reduce recurrent PMB.

- **Chapter 6** presents an economic analysis, which is performed alongside the RCT.

- **Chapter 7** shows the results of a systematic review on the diagnostic accuracy of outpatient endometrial sampling when compared to the golden standard hysteroscopy or hysterectomy.

- In the final chapters, **chapter 8 and 9**, this study comes full circle. These chapters highlights the most important findings and answer the overarching questions in a summary of this thesis. They discuss limitations of this study and they also reflect on the clinical implications of these findings. Finally, they outline suggestions for further research.

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Chapter 2

Diagnostic evaluation of the endometrium in postmenopausal bleeding: an evidence-based approach

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M.P.M. Burger, B.W.J. Mol & A. Timmermans

Maturitas 2011 Feb; 68(2): 155-64

Abstract

Postmenopausal bleeding (PMB) is a common complaint in general gynaecological practice. Women with PMB have around a 10% chance of having endometrial cancer and therefore PMB always needs further evaluation. This article summarises the reviews on the subject and provides an overview of the use of diagnostic tools in patients with PMB. Four types of diagnostic test are described: sonographic measurement of endometrial thickness, endometrial sampling, hysteroscopy and saline infusion sonography. All four have been independently shown to be accurate in excluding endometrial cancer. However, neither in systematic reviews nor in international guidelines is consensus found regarding the sequence in which these methods should be employed in women with PMB. For measurement of endometrial thickness in symptomatic women, a cut-off value of three millimetres is recommended, but the cost-effectiveness of this strategy has yet to be shown. Research should now focus on the incorporation of individual patient characteristics and pre-test probabilities for cancer in algorithms for the investigation of PMB, and the most cost-effective sequenced combination of the four types of tests.

Introduction

Postmenopausal bleeding (PMB), defined as blood loss occurring at least 12 months after menopause, is a common complaint in general gynaecological practice. The prevalence of PMB is approximately 10% immediately after menopause.[1] Postmenopausal bleeding (PMB) signals endometrial cancer in around 10% of cases,[2,3] or less serious conditions, such as benign endometrial polyps, in a further 20 to 40%.[2,4,5] Endometrial cancer is the most common gynaecologic cancer and 95% of women with endometrial cancer present with PMB.[6,7] 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. Any PMB needs further investigation.

In the past, the principal method of investigation was dilatation and curettage (D&C).[8] To reduce the invasiveness of investigatory procedures, ultrasonography was introduced. Endometrial biopsy and hysteroscopy have now almost completely replaced D&C. The use of outpatient endometrial biopsy reduces costs in the diagnostic work-up, without affecting life expectancy.[9] Despite many studies on the investigation of PMB, there is still no consensus on the most accurate and efficient diagnostic pathway.[7,10-13] This article describes a systematic literature search for guidelines and systematic reviews on this subject. The aim is to recommend an evidence-based diagnostic pathway for patients with PMB.

Methods

Identification of studies

We performed a computerised MEDLINE and EMBASE search to identify all studies on the evaluation of PMB published between January 1965 and January 2010. The search was limited to human studies; language restrictions were not applied. We included systematic review articles of observational studies on the evaluation of the endometrium in women with PMB. In addition we searched for national and international guidelines on this subject. References cited in the selected reviews were checked for further relevant articles not identified by the electronic searches. We used all known synonyms for the following keywords: postmenopausal bleeding, endometrial thickness, ultrasound, hysteroscopy and biopsy. The search strategies for the two databases are detailed in Appendices A and B.

Selection criteria

This review focused on systematic reviews in which the results of the diagnostic test of interest were compared with the results of a reference standard. The following criteria were used to select articles:

1. Population of interest was women with postmenopausal uterine bleeding.
2. The four types of diagnostic test of interest were: (a) measurement of endometrial thickness by transvaginal sonography (TVS); (b) outpatient endometrial sampling; (c) saline infusion sonography (SIS); or (d) hysteroscopy (i.e. endoscopic visual interpretation).
3. The reference standard was the endometrial histological findings from inpatient endometrial sampling, D&C or hysterectomy.
4. The primary outcome measure was the accuracy with which endometrial cancer and/or hyperplasia were diagnosed.

Studies in which more than 10% of the women used Tamoxifen were excluded, because of different pathophysiology and different characteristics of the uterine cavity. For studies that included pre- and postmenopausal women we used only those calculations and conclusions concerning the latter. The systematic reviews were selected by two reviewers working independently (NvH and MCB), through assessment of the titles and abstracts of all retrieved studies. In case of disagreement the article was included for full reading and/or assessed by a third reviewer (AT).

Additionally, we identified national and international guidelines on diagnostic procedures for PMB. From every guideline we extracted the diagnostic pathway recommended and points of policy.

Quality assessment

The methodological quality of each selected paper was assessed using the Cochrane checklist for systematic reviews of diagnostic studies.[14] This list of criteria was designed to assess the usability of a review for guideline development. Because there is no validated checklist for the quality assessment of systematic reviews, this checklist was used as an aid in the reviewers' evaluation of the quality of the original review, but no decisions regarding the inclusion or exclusion of articles were based on this assessment.

Data extraction, analysis and interpretation

From each systematic review or meta-analysis we extracted (if available) figures for the sensitivity, specificity, likelihood ratios (LRs), the pre-test probability of endometrial cancer and/or hyperplasia and the post-test probability. If an article described both post- and premenopausal women we extracted the data relating to the postmenopausal women. We used only data from studies evaluated as high quality by the reviewers.

The LR indicates by how much a specific test raises or lowers the probability of having endometrial pathology. An LR of 1 indicates that the test has no predictive value for the outcome of interest. The higher an LR is above 1, the larger is the probability of pathology. An LR of less than 1 indicates that a negative test result is more likely to be true. In the present study, for a rating of 'high' diagnostic accuracy, the LR had to be over 10 for a positive test result or less than 0.1 for a negative result[15]. In this article, we use the LR of a negative test result (LR−) for reviews on the use of TVS, because we are interested in its accuracy in excluding endometrial cancer. For endometrial sampling and hysteroscopy we are interested in diagnosing cancer, so we used the LR of a positive test (LR+) and calculated the post-test probability of a positive test. When an article did not report post-test probability, we used Bayes' theorem to calculate the post-test probability, using the following formula:

$$\text{post-test probability} \quad \frac{\text{LR} \times (\text{pretest probability} / (1\text{-pre-test probability}))}{(\text{LR} \times (\text{pretest probability} / (1\text{-pre-test probability}))) + 1}$$

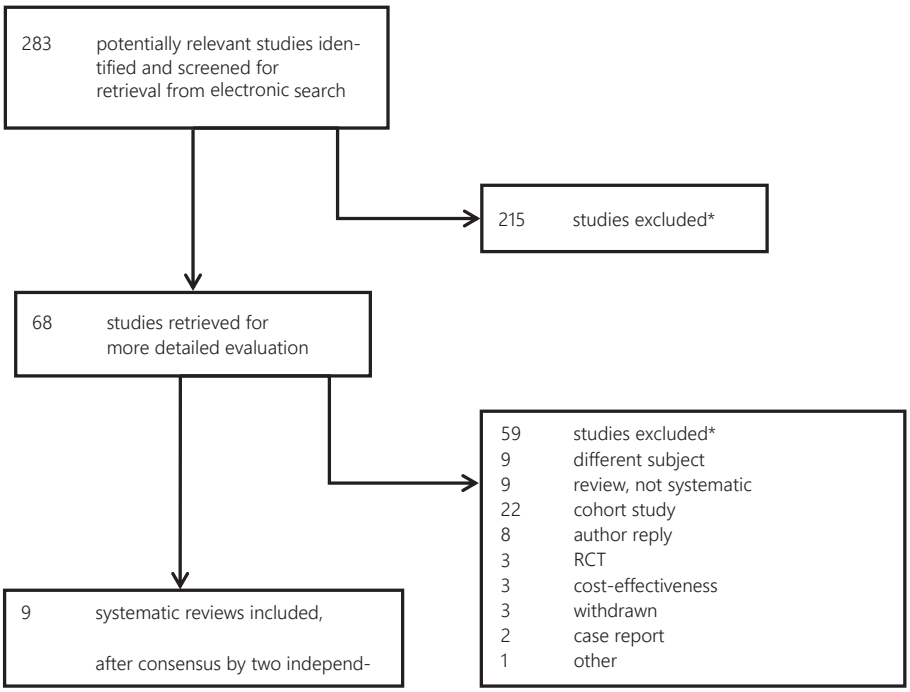
To compare study results we used pre-test probabilities extracted from the literature: a probability of 10% for endometrial cancer and a probability of 40% for focal benign or (pre)malign endometrial disease.[16,17]

Results

Study selection

A total of nine systematic reviews assessed (part of) the diagnostic pathway for women with PMB and met the criteria for inclusion (Figure 1). Of the selected systematic reviews, four articles assessed the use of TVS, [16,18-20] one described the use of SIS[21], two assessed the use of outpatient endometrial sampling[22,23] and two assessed the use of hysteroscopy in patients with abnormal uterine bleeding.[24,25] Table 1 shows further details of these studies.

Figure 1. Study selection diagram



* The reference list for excluded studies is available from the corresponding author.

Five of the selected reviews included both pre- and post- menopausal women.[21-25] For this review, we used only the calculations and conclusions concerning postmenopausal women. The diagnostic accuracy reported in all included reviews is shown in Table 2. Additionally, we identified a set of five national and international guidelines concerning diagnostic strategies for PMB.[7,10-13]

Table 1. Studies about accuracy of diagnostic tests in women with PMB

Author	Year	Type of study	Studies (N)		Patients (N)			Subject	Failure/ inadequate		Reference test
			Total	PMP	Total	PMP	HRT		Overall	PMP	
Smith-Bindman et al.	1998	systematic review meta-analysis	35	35	5892	5892	8.0%	TVS	0%	0%	endometrial sampling or D&C or hysterectomy
Tabor et al.	2002	systematic review meta-analysis	9	9	3813	2700	0.0%	TVS	n/a	n/a	D&C or endometrial sampling
Gupta et al.	2002	systematic review meta-analysis	57	4	7270	464	1.3%	TVS	n/a	n/a	endometrial sampling or D&C or hysterectomy
Timmermans et al.	2010	syst review IPD meta-analysis	11	11	2896	2896	n/a	TVS	n/a	n/a	histology (different methods)
Clark et al.	2001	systematic review meta-analysis	6	2	881	220	n/a	biopsy	4%	2%	histology (by inpatient sampling)
Dijkhuizen et al.	2000	systematic review meta-analysis	39	7	7814	760	n/a	biopsy	0-41%	0-54%	D&C or hysteroscopy or hysterectomy
de Kroon et al.	2003	systematic review meta-analysis	24	n/a	2278	268	<5%	SIS	7%	n/a	hysteroscopy or hysterectomy
Clark et al.	2002	systematic review meta-analysis	65	2	26346	1948	4.3%	hysteroscopy	3.6%	3.4%	histology (different methods)
van Dongen et al.	2007	systematic review meta-analysis	17	5	4208	306	<5%	hysteroscopy	3.2%	4.4%	histology (different methods)

n/a = not applicable
PMP = postmenopausal women
* pre- and postmenopausal women

Table 2. Diagnostic accuracy of diagnostic tests in women with PMB

Study	Subject	Outcome measure	Cut-off value or device	Sens* (%)	Spec* (%)	LR+*	LR-*	Pre-test probability*	Post-test probability*
Smith-Bindman	TVS	endometrial cancer	5 mm	96.0	61.0		0.07	10.0%	1.0%
		endometrial cancer	4 mm	96.0	53.0		0.08	10.0%	0.8%
		endometrial cancer	3 mm	100.0	38.0		0.00	10.0%	0.0%
		endometrial disease	5 mm	95.0	92.0		0.05	40.0%	3.5%
		endometrial disease	4 mm	91.0	69.0		0.13	40.0%	8.0%
		endometrial disease	3 mm	98.0	62.0		0.03	40.0%	2.11%
Tabor	TVS	endometrial cancer	MoM	96.0	50.0		0.08	10.0%	0.9%
Gupta ‡	TVS	endometrial cancer	5 mm	91.7	66.1		0.16	10.0%	2.5%
		endometrial cancer	4 mm	n/a	n/a		n/a	n/a	n/a
		endometrial disease	5 mm	95.7	77.5		0.08	40.0%	5.1%
		endometrial disease	4 mm	n/a	n/a		n/a	n/a	n/a
Timmermans	TVS	endometrial cancer	5 mm	90.3	54.0		0.18	10.0%	2.0%
		endometrial cancer	4 mm	94.8	46.7		0.11	10.0%	1.2%
		endometrial cancer	3 mm	97.9	35.4		0.06	10.0%	0.7%
Clark	sampling	endometrial cancer¥	all devices	91.9	99.7	95.1		4.5%	81.8%
		hyperplasia	all devices	81.0	98.9	73.6		14.3%	66.7%
		hyperplasia	Pipelle	n/a	n/a	n/a		14.3%	62.3%
Dijkhuizen	sampling	endometrial cancer	all devices	95.0	99.5	190.0		10.0%	95.5%
		endometrial cancer	Pipelle	99.6	n/a	n/a		n/a	n/a
		hyperplasia	Pipelle	88.0	98.0	44.0		14.3%	88.0%
de Kroon	SIS	abnormal cavity	n/a	95.0	88.0	n/a	n/a	n/a	n/a
Clark	hysteroscopy	endometrial cancer ¥	n/a	86.4	99.2	60.9		3.9%	71.8%
		endometrial cancer (PMP)	n/a	n/a	n/a	38.3		10.0%	64.8%
van Dongen¥	hysteroscopy	abnormal cavity	n/a	96.0	90.0	7.9		61.0%	93.0%

n/a = not applicable or not available; MoM = multiples of the median; PMP = postmenopausal.

* Bold when extracted from article, normal when calculated, italic when extracted from literature.

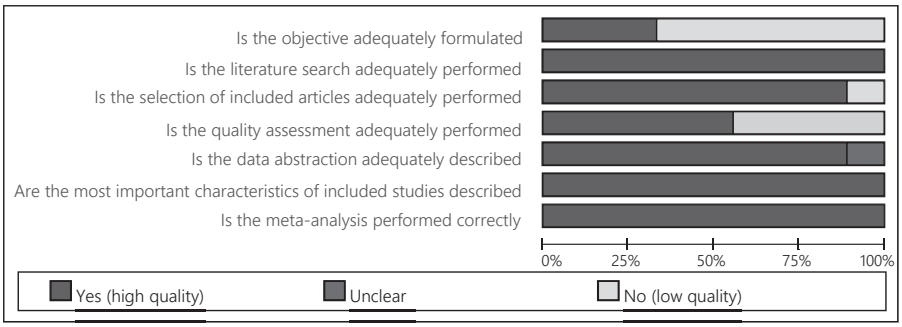
‡ For the cut-off value of 4 mm, no studies included with good quality.

¥ Pre- and postmenopausal women.

Quality assessment

The results of the quality assessment are reported in Figure 2. Overall, study quality was good. The quality of the formulation of the objective was rated as moderate (according to the checklist, studies scored well on this item if they described the patient population, the intervention, the reference standard and the desired result). All studies scored positively on items concerning the literature search, description of study characteristics and correctly performed meta-analysis. Study quality assessment was adequately performed in 55% (5/9) of the reviews.

Figure 2. Methodological quality of included studies



Transvaginal sonography

The main goal of TVS is to exclude endometrial cancer. Almost every guideline refers to a meta-analysis performed in 1998 by Smith-Bindman et al[16] 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 cancer. Only 16 of the 35 included studies reported the number of women who could not tolerate TVS (mean 0%) and only 14 studies reported non-diagnostic results (mean 0%). With a cut-off value of 5 millimetres (mm), the sensitivity for detecting endometrial cancer 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 of TVS reached different conclusions, however.[18-20] Tabor et al conducted a meta-analysis of nine studies.[18] They included studies only if the corresponding author was able to supply original data. For each included study, the median endometrial thickness per centre 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 centres, 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[16], 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.[19] 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 21) used a ≤5 mm cut-off, but these employed the best quality criteria. Pooling of the results of these four studies resulted in a LR− of 0.16. This LR 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 of ≤5 mm.

In conclusion, the meta-analyses done by Tabor, Gupta and Smith-Bindman are limited because they are based on previously published data, and probably overestimate the accuracy of predictions based on endometrial thickness. With respect to meta-analysis of randomised trials, individual patient data are considered to be superior to meta-analysis of the literature.[26] 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[20] 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 LR 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.

Outpatient endometrial sampling

Clark et al conducted a systematic review and meta-analysis to determine the diagnostic accuracy of outpatient endometrial sampling in detecting endometrial hyperplasia.[22] Postmenopausal women were included in two studies, in which they represented 25% of the (combined) patient sample. In these two articles three different diagnostic devices had been used for endometrial sampling: Accurette®, Pipelle® and Vabra® aspirator. The pre-test probability of 14.3% was increased to a post-test probability for a positive result of 66.7% (95% CI 42.3–83.9%). In 34 of 149 women the endometrial sampling was unsuccessful, with a failure rate (sampling not possible for technical reasons) of 17% (25/149) and an inadequate sampling rate (not enough tissue obtained for a pathologic diagnosis) of 7% (9/124). This review demonstrated that endometrial sampling is moderately accurate in diagnosing (pre) malignant endometrial pathology. A positive test result was more accurate than a negative test result (sensitivity 91.9%, with a specificity of 99.7%). Clark et al concluded that the more clinically significant the endometrial pathology is, the better the diagnostic accuracy of outpatient endometrial sampling will be and, hence, the more clinically useful the test. Additional endometrial assessment should be undertaken with technical failure or inadequate sampling, especially if symptoms persist.[22]

Dijkhuizen et al performed a meta-analysis to assess the accuracy of endometrial sampling devices in the detection of endometrial cancer and atypical hyperplasia.[23] With respect to the diagnosis of endometrial cancer, they identified seven studies that were limited to postmenopausal women. The pooled data from these studies showed a sensitivity of 95% and a specificity of 99.5%, giving a post-test probability for a positive test of 95.5%. Outpatient endometrial sampling therefore appeared to be a highly sensitive technique for diagnosing endometrial cancer. With regard to inadequate sampling (0 to 54% of cases in the studies they reviewed), they concluded that an inadequate sample is an indication for further investigation, based on an article of Farrell et al which demonstrated that of those women for whom the result of the Pipelle was 'insufficient' 20% had uterine pathology after further investigation, 3% with endometrial cancers.[27]

Saline infusion sonography

Only one systematic review, by de Kroon et al has described the evaluation of the diagnostic accuracy of SIS in pre- and post- menopausal women with abnormal uterine bleeding.[21] The main outcome measures were LRs, post-test probabilities and the success rate of SIS in the prediction of uterine cavity abnormality. We focus here on the results regarding women with PMB. The review identified 24 studies with homogeneous data, but only five of these concerned postmenopausal women. Pooling the data from these five articles gives a sensitivity of 95% and a specificity of 88%. The calculations for endometrial cancer were not mentioned. Sensitivity and specificity were not separately described for pre- and postmenopausal women, but the overall success rate was significantly lower in postmenopausal women: 87%, compared with 95% for premenopausal women ($P < 0.01$).

Hysteroscopy

Clark et al 2002 performed a systematic quantitative review in which they focused on the diagnostic accuracy of hysteroscopy in diagnosing endometrial cancer or hyperplasia.[24] Postmenopausal women represented 29% of the populations studied. Only two studies concerning postmenopausal women were rated as high quality. Pooled data from these showed a post-test probability of a positive test of 71.8% (95% CI 67.0–76.6%). In these studies the failure rate for hysteroscopy (ambulant or inpatient) was 3.4% (67 of 1948 women), which was comparable with the overall failure rate in premenopausal women. 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[25] This article focused on studies of 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.[24] In this review five studies of postmenopausal women with homogeneous data were included. The pooled sensitivity and specificity in the assessment of uterine cavity abnormality 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. When a patient presents with PMB the first step in every guideline is referral to a gynaecologic practice for examination, pap smear and TVS. Only the US guidelines[10,12] recommend either TVS or outpatient endometrial sampling as the first step in diagnosing women with PMB, based on similar sensitivities and cost-effectiveness for the detection of endometrial cancer for an endometrial thickness of 5 mm or more and for endometrial sampling when 'sufficient' tissue is obtained.[16,28] In the other guidelines 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 to 5mm. These cut-off points are mostly based on the meta-analysis by Smith-Bindman,[7,10,12,16] but also on Swedish literature,[11] and the review by Gupta et al[19] The most important issue is what probability of endometrial cancer is deemed acceptable after a negative test.

In the US guidelines, endometrial sampling is recommended with a cut-off value for the endometrial thickness of 5 mm and at the same time they recommend TVS when the endometrial sampling is deemed 'insufficient'. SIS is used to distinguish between a diffusely thickened endometrium, for which D&C could be the next step,[12] and between a focal lesion, for which a hysteroscopy is the next advised step.[10,12] The National Guideline Clearinghouse stated that D&C in women with PMB should be performed only when endometrial sampling is indicated and cannot be performed or is inconclusive and sonographic techniques are non-reassuring. D&C should always have concomitant hysteroscopy, in case of focal pathology.[11]

The European guidelines advise 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.[7,11,13] With focal lesions the recommendation is to perform a (therapeutic) hysteroscopy and with diffuse lesions D&C, but only when endometrial sampling is insufficient or has failed. 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.[13]

With recurrent or persistent PMB there are different strategies. In the Dutch guideline immediate hysteroscopy is advised;[7] the Swedish guideline advises outpatient endometrial sampling or, if technically not possible, D&C.[11] The further investigation and management of benign lesions in women with PMB require more research. The question is whether the treatment of benign lesions improves the patient's quality of life, morbidity and survival.[7,12]

Discussion

The goal of this systematic review was to produce an evidence-based diagnostic pathway for patients with PMB. The most important conclusion is that in neither systematic reviews nor international guidelines can consensus be found regarding the sequence in which the different procedures should be implemented. All four types of test have been shown to be accurate and feasible in excluding or diagnosing endometrial cancer, by their high sensitivities and specificities.

Based on the available evidence, discussed in this review, we can conclude that TVS is an accurate method to exclude endometrial cancer, although there is still debate over the best cut-off value for endometrial thickness that should warrant endometrial sampling. Based on the highest sensitivity, a cut-off value of 3 mm is recommended, but the cost-effectiveness of this value has yet to be demonstrated.

Regarding the use of outpatient endometrial sampling, the two included reviews showed the high accuracy of this diagnostic method.[22,23] Clark et al focused mainly on hyperplasia,[22] while Dijkhuizen et al concluded that outpatient endometrial sampling is an accurate method for excluding cancer in women with PMB.[23] However, the technique had a high rate of insufficient or failed sampling (0–54% in different observational studies).[22,23] An insufficient sample should be an indication for further investigation.[22,27,30] From the available reviews we cannot draw conclusions regarding the sequence of the tests in the diagnostic pathway of PMB. All the studies evaluated the tests independently, without any consideration of combinations of tests or previous test results.

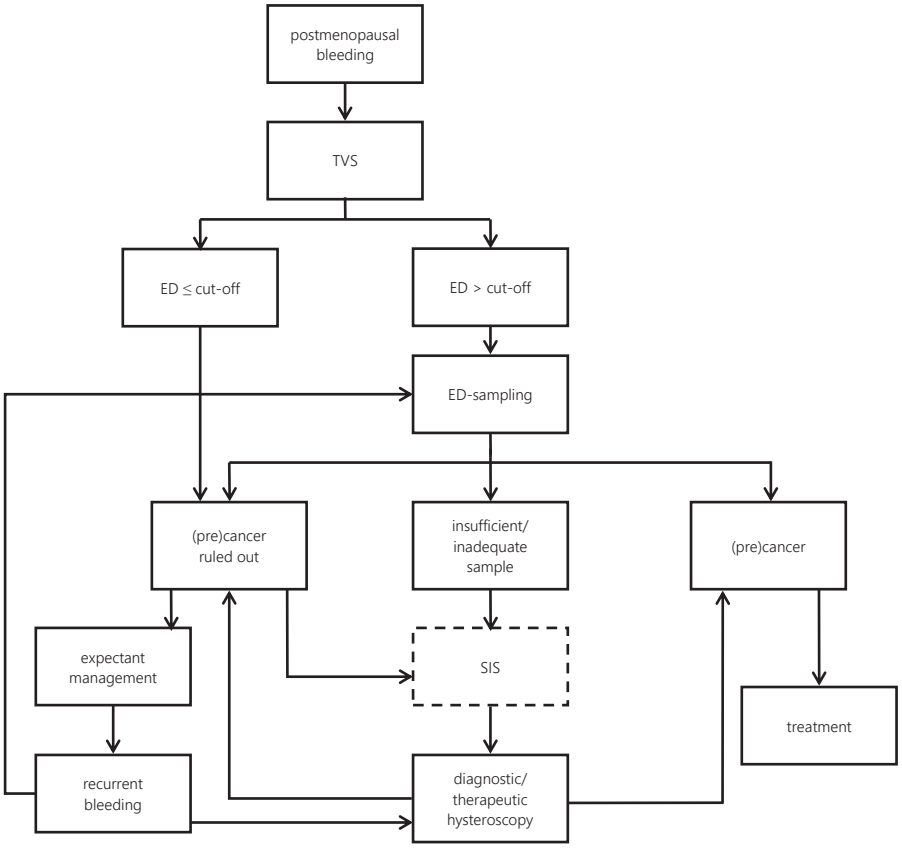
In determining the best sequence of tests, different factors have to be taken into account, such as cost-effectiveness, the prevalence of endometrial cancer, local logistics (the availability of ultrasound, the use of outpatient endometrial sampling and

the use of outpatient hysteroscopy), as well as doctor and patient preferences. The preferences of doctors in relation to diagnostic procedures for endometrial cancer in women with PMB have not been investigated. Furthermore, guidelines need to meet the expectations of the patients; most women want to rule out endometrial cancer with a certainty of 100% and they are prepared to undergo rather invasive and painful diagnostic tests in order to achieve this.[31] However, a post-test probability of 0.0% seems virtually impossible and one should also keep in mind that the risk of endometrial cancer in a population of asymptomatic postmenopausal women is reported to be 0.2%.[32]

Clark et al determined the most cost-effective strategy for diagnosing endometrial cancer.[29] They constructed a decision model and evaluated 12 different strategies for the initial investigation of PMB. With a cancer probability of 10%[16,17] the strategy with TVS as the initial test with a cut-off of 4 mm followed by endometrial sampling was most cost-effective. Unfortunately, a cut-off value of 3 mm was not considered in their evaluation. More importantly, in this decision model, the assumptions made regarding test accuracy were based on the available systematic reviews. Systematic literature reviews in diagnostic research report the accuracy of tests, and thereby assist clinicians in their decision-making. However, there are limitations to this approach, as the analysis of such data often does not allow reviewers to explore the diagnostic information gained from combinations of tests. In clinical practice, tests are commonly combined in diagnostic sequences and disease probabilities are usually estimated in a hierarchical manner, first combining information from the history and examination, followed by additional information obtained from other diagnostic procedures (e.g. TVS, endometrial sampling). Studies of test accuracy often do not take this clinical paradigm into account, but tend to report test results in isolation and disregard the history and examination. In addition, they usually analyse a single test at a time, without taking into account of what is known from previous testing.

There is considerable variability in endometrial thickness and the likelihood of endometrial cancer across women. Individual patient characteristics, including age, time since menopause, obesity, hypertension, diabetes mellitus and reproductive factors, are associated with a higher prevalence of endometrial cancer.[33-38] However, current policy is not based on these risk factors, but only on endometrial thickness.[7,10-13] Breijer et al developed an algorithm for diagnostic pathways in women with PMB.[39] This algorithm includes the calculation of the pre-test probability of endometrial cancer based on individual patient characteristics and the diagnostic approach to benign pathology, both of which require further research.

Figure 3. Possible diagnostic pathway in postmenopausal bleeding



The dashed box shows that SIS can be used to distinguish between focal and diffuse pathology before performing a hysteroscopy, according to the local protocol.

Future research should also aim to maximise accuracy in relation to cost-effectiveness for the different methods. Incorporation of a combination of endometrial thickness and patient characteristics within a single diagnostic pathway increased diagnostic accuracy in some studies.[40-42] Future research has to focus on the combination of different diagnostic tests as well as the incorporation of patient characteristics, rather than on the diagnostic accuracy of a single test. Furthermore, by combining and analysing individual patient data from different studies (i.e. meta-analysis of individual patient data), larger databases can be obtained, in which previously described models can be externally validated.[40-43]

We can conclude that the first step in the diagnostic pathway should be the measurement of endometrial thickness, using a cut-off point of 3 or 4 mm, followed by endometrial sampling. Figure 3 shows an algorithm with an evidence-based diagnostic pathway for women with PMB. Only when TVS is not readily available should direct endometrial sampling be an option. For further investigation when the sample is insufficient or when it is unsuccessful, SIS can be used to distinguish between focal and diffuse pathology. Hysteroscopy should be used as the final step in the diagnostic pathway of women with PMB.

Conclusions

- Neither in systematic reviews nor in international guidelines is consensus found regarding the best sequence of diagnostic procedures for women with PMB.

- Measurement of endometrial thickness, endometrial sampling and hysteroscopy have been independently shown to be accurate in excluding endometrial cancer.

- In relation to endometrial thickness, a cut-off value of 3 or 4 mm is recommended, but the cost-effectiveness of this strategy has yet to be demonstrated.

Appendix A and B

Appendix A: Search strategy - Medline

#	Searches
1	Postmenopause/
2	postmenopau*.tw.
3	post-menopau*.tw.
4	or/1-3
5	exp Hemorrhage/
6	(bleed* or hemorrhag* or haemorrhag* or blood loss*).tw.
7	or/5-6
8	4 and 7
9	hysteroscopy/
10	hysteroscop*.tw.
11	or/9-10
12	Biopsy/ or Biopsy, Needle/
13	exp Curettage/
14	(biop* or curett* or pipelle*).tw.
15	or/12-14
16	ultrasonography/ or endosonography/ or exp ultrasonography, doppler/
17	vagina/us or endometrium/us or Uterine Hemorrhage/us or exp Uterine Neoplasms/us or exp Uterine Diseases/us
18	((endometr* or vagina* or endovagin* or transvagina* or trans-vagina* or endo-vagi* or uter* or intrauter* or intra-uteri*) adj6 (echo* or ultrasound or ultrasono* or sonograph* or doppler or endoscop* or endoson*)).tw.
19	(hysterosalpingogr* or hysterosonogra*).tw.
20	thick*.tw.
21	or/16-20
22	11 or 15 or 21
23	8 and 22
24	exp "sensitivity and specificity"/
25	(diagnos* or test or tests or exclude or value or role or evaluation).ti.
26	(accurac* or (sensitivit* and specificit*) or (predictive adj3 value*1) or (false adj2 (negative or positive)) or ROC or pretest or validat*).tw.

27	or/24-26
28	11 or 15 or 21 or 27
29	28 and 8
30	(meta-analysis.pt. or exp technology assessment, biomedical/ or (((hta or health technology) adj6 assessment*) or meta analy* or metaanaly* or meta?analy*).tw. or (cochrane or evidence or EBM).jw. or ((review* or search*) adj10 (literature* or medical database* or medline or pubmed or embase or cochrane or cinahl or psychinfo or psychlit or healthstar or biosis or current conten* or systemat*)).tw.) not (comment or editorial or historical-article).pt.
31	29 and 30
32	29
33	limit 32 to yr="2008 -Current"
34	33 not 31
35	review.pt.
36	(review or overview).ti.
37	35 or 36
38	34 and 37
39	34 not 37
40	("11042572" or "19576369" or "17516956" or "12039131" or "9809732" or "12350192" or "12225294" or "14550365").an.
41	40 and 31
42	40 and 38
43	from 31 keep 1-59
44	from 38 keep 1-4
45	from 39 keep 1-115

Appendix B: Search strategy - Embase

#	Searches
1	Postmenopause/
2	(postmenopau* or post-menopau*).tw.
3	(after menopaus* or after the menopaus* or following menopaus* or following the menopaus*).tw.
4	(older adj2 (wom#n or female*)).tw.
5	or/1-4

6 exp bleeding/
7 (bleed* or hemorrhag* or haemorrhag* or blood loss*).tw.
8 or/6-7
9 5 and 8
10 hysteroscopy/
11 hysteroscop*.tw.
12 or/10-11
13 biopsy.mp.
14 curettage/
15 (biop* or curett* or pipelle*).tw.
16 or/13-15
17 exp echography/
18 hysteroscopy/ or hysterosalpingography/ or hysterography/
19 thickness/
20 ((endometr* or vagina* or endovagin* or transvagina* or trans-vagina* or endo-vagi* or
uter* or intrauter* or intra-uteri*) adj6 (echo* or ultrasound or ultrasono* or sonograph* or
doppler or endoscop* or endoson*)).tw.
21 (hysterosalpingogr* or hysterosonogra*).tw.
22 thick*.tw.
23 or/17-22
24 diagnostic accuracy/ or diagnostic test/ or diagnostic value/ or exp diagnostic error/ or roc
curve/ or "sensitivity and specificity"/ or validity/ or predictive validity/
25 (diagnos* or test or tests or exclude or value or role or evaluation).ti.
26 (accurac* or (sensitivit* and specificit*) or (predictive adj3 value*1) or (false adj2 (negative or
positive)) or ROC or pretest or validat*).tw.
27 or/24-26
28 12 or 16 or 23 or 27
29 28 and 9
30 uterus bleeding/di or vaginal bleeding/di
31 30 and 5
32 29 or 31

33 exp meta analysis/ or exp Literature/ or exp Biomedical Technology Assessment/ or (hta or (health technology adj6 assessment*) or metaanaly* or meta analy* or meta?analy*).tw. or (cochrane or evidence or EBM).jx. or ((review* or search*) adj10 (literature* or medical data base* or medline or pubmed or embase or cochrane or cinahl or psychinfo or psychlit or healthstar or biosis or current content* or systematic*)).tw.

34 32 and 33

35 limit 32 to yr="2008 -Current"

36 35 not 34

37 review.pt.

38 (review or overview).ti.

39 37 or 38

40 36 and 39

41 36 not 39

42 ("2009314425" or "2007250425" or "2003399129" or "2002343827" or "2002331806" or "2002111470" or "2000376745" or "1998375444").an.

43 42 and 34

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Chapter 3

Prediction models in women with postmenopausal bleeding: a systematic review

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Abstract

Postmenopausal bleeding is associated with an elevated risk of having endometrial cancer. The aim of this review is to give an overview of existing prediction models on endometrial cancer in women with postmenopausal bleeding. In a systematic search of the literature, we identified nine prognostic studies, of which we assessed the quality, the different phases of development and their performance. From these data, we identified the most important predictor variables. None of the detected models completed external validation or impact analysis. Models including power Doppler showed best performance in internal validation, but Doppler in general gynaecological practice is not easy accessible. We can conclude that we have indications that the first step in the approach of women with PMB should be to distinguish between women with low risk versus high risk of having endometrial cancer and the next step would be to refer patients for further (invasive) testing.

Introduction

Endometrial cancer is the most common gynaecologic cancer. Approximately 95% of women with endometrial cancer present with postmenopausal bleeding (PMB).[1, 2] PMB signals endometrial cancer, which is present in about 10% of cases,[3, 4] or less serious conditions, such as benign endometrial polyps or endometrial atrophy.[3, 5-7]

To reduce invasive procedures in women with PMB, measurement of the endometrial thickness is used to stratify women into low versus high risk of having endometrial cancer. Measurement of endometrial thickness has shown to be accurate in excluding endometrial cancer, although the risk of endometrial cancer with a negative test is still 0.7-3.5% depending on the cut-off point used.[8, 9]

In women with PMB there is considerable variability in endometrial thickness and the likelihood of endometrial cancer.[10] Individual patient characteristics including age, time since menopause, obesity, hypertension, diabetes mellitus and reproductive factors, are associated with a higher risk of endometrial cancer.[10-16] While the probability of postmenopausal bleeding decreases with increasing age,[17] 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 to 24% in women older than 80 years.[18]

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 pre-test probability, which is altered by patient's 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.[2, 19-21]

Clinical doctors want to identify women with a high risk for endometrial cancer when presenting with PMB. Several articles have studied this subject and developed models to estimate the individual chance of endometrial cancer in women presenting with PMB. The purpose of this review is to give an overview of the existing prediction models for endometrial cancer in women with PMB, to assess their quality and to identify important predictor variables.

Methods

Study identification

We performed a computerized MEDLINE and EMBASE search to identify all studies on prediction models in women with postmenopausal bleeding published from inception to June 2011. The search was limited to human studies, no restrictions were held concerning publication year or language. We included articles reporting on multivariable models predicting endometrial cancer in women with PMB. We checked references cited in the selected articles for further relevant prediction models not identified by the electronic searches. We used all known synonyms for the terms 'postmenopausal bleeding' and 'endometrial cancer' and we used a search-filter for prediction models.[22] The search strategy can be found in Appendix 1.

Study selection

This review focused on articles that report on a prediction model for endometrial cancer in women with PMB. In this review, a prediction model was defined as a multivariable model that expresses the chance of endometrial cancer as a function of two or more predictor variables. PMB was defined as vaginal bleeding after more than one year of amenorrhea after the age of 40 or persistent (>3 months) unscheduled bleeding on hormone replacement therapy (HRT). Two independently working reviewers (NvH and MB) selected the articles, by assessing titles and abstracts. If there were any doubts about eligibility after reading title and abstract, we read the full text version to make sure no articles were missed. In case of disagreement the article was included for full text reading and assessed by a third reviewer (AT).

Study quality assessment

A framework for quality assessment was developed based on the recommendations of Hayden et al[23] and on a quality assessment framework for prediction models in subfertile women to predict the chance of pregnancy.[24] The framework was divided into four sections: study participation, predictor variables, outcome measurement and analysis. Each item in the different sections was scored with 'yes', 'no' or 'unclear'.

Predictor variables

All predictor variables were collected for each prediction model. The predictor variables are the potential predictors, which were tested, both during model development and in the final model. The original articles selected multiple variables or risk factors,

which are thought to be associated with an increased risk of endometrial cancer. These variables have been tested in the original articles for univariate association and, if sufficiently contributing to predictive accuracy in multivariable regression analysis, combined to construct a clinical prediction model. We collected all different predictor variables from the original articles, together with their significance, to identify the most important predictor variables for endometrial cancer. The most important predictor variables had been considered as statistically significant input variables in three or more studies or were considered statistically significant in two studies and had not been tested in other studies.

Model development assessment

The development of a prediction model consists of three phases: model derivation, model validation and impact analysis.[25] In the first phase, model derivation, predictor variables are identified by logistic regression. Model validation, the second phase, consists of an internal and external validation phase.[24] In internally validated models, the performance of the model is tested in the same data set in which the model was developed, or in a group of subsequent patients within the same centre. In external validation, the goal is to demonstrate generalizability and reproducibility in patients different from the patients used for derivation of the original model. Therefore, the prediction model is evaluated on new data collected from an appropriate patient population in a different centre.[26] The final phase of model development is impact analysis, in which prediction models are tested for their ability to change clinician's decisions and to change patient outcomes.[27] All prediction models identified in this review are classified into the different phases of model development. We sent an email to all authors of the identified articles to investigate if their models are undergoing external validation and are not published yet.

Model performance

Performance measures (calibration, discrimination and clinical usefulness) and the range of probabilities given by the different prediction models were recorded. Calibration refers to the agreement between observed probabilities and predicted probabilities for groups of patients; this is usually reported as a calibration plot or a Hosmer-Lemeshow statistic (test for 'goodness-of-fit').[28] Discrimination is commonly reported as the c-statistic (concordance), also referred to as the Area Under the receiver-operating characteristic Curve (AUC). It measures the ability of a prediction model in separating patients with endometrial cancer and patients without

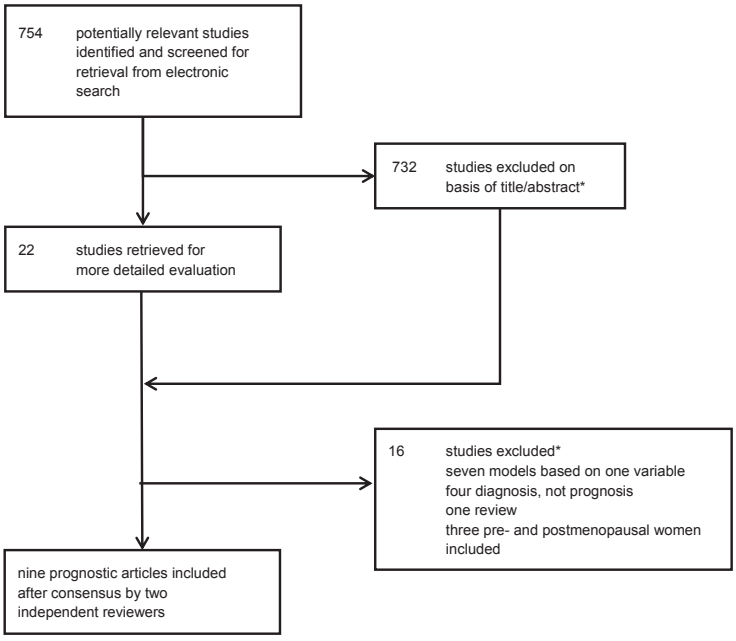
endometrial cancer. An AUC of 0.5 describes a non-informative test, whereas an AUC of 1.0 represents a test that discriminates perfectly between presence and absence of a disease.[29] Clinical usefulness measures how close a prediction for an individual patient is to her actual outcome. This is mostly reported as accuracy (percentage of patients correctly classified), sensitivity or specificity, positive or negative predictive value (PPV or NPV) or likelihood ratios (LR) of a prediction model.[30] As we are interested in identifying a group of patients with a high risk for endometrial cancer, we are most interested in a high sensitivity, high NPV and a low negative LR.

Results

Study identification and selection

Of 754 articles identified by the MEDLINE and EMBASE search, a total of nine articles met the inclusion criteria of our review.[31-39] We identified another three articles by scanning the reference lists of included articles,[40-42] however none of these matched our inclusion criteria after reading the abstract and full text version of these articles (Figure 1).

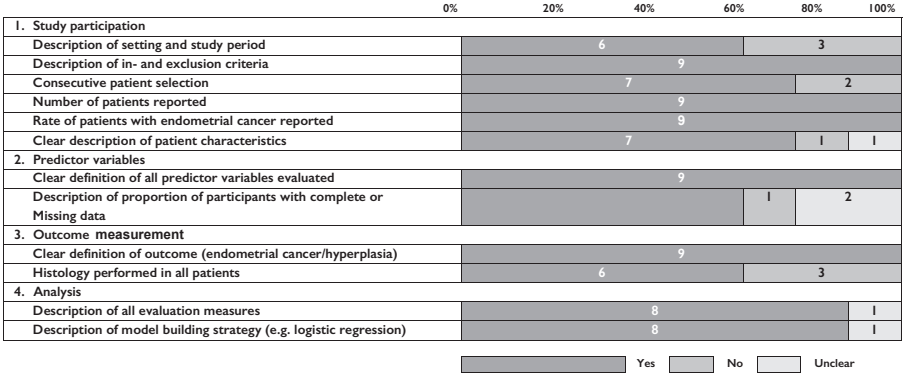
Figure 1. Study selection diagram



Study characteristics

Study characteristics are shown in Table 1. Of the nine selected articles on prediction models for women with PMB, five articles described the development of one model and four articles described two or more different prediction models. In the nine selected articles, four models were based primarily on patient characteristics,[31, 34, 36, 38] four prediction models were based on a combination of patient characteristics and grey-scale transvaginal sonography (TVS) findings,[31, 33, 36] two prediction models were based on a combination of patient characteristics, hysteroscopy and/or grey-scale TVS findings,[31] two prediction models were based on TVS findings only[37, 39] and three models used Doppler TVS findings as a predictor variable.[35, 37, 38] Patient selection and inclusion criteria were not the same in all articles. All nine articles included women with PMB, but three of these articles studies a population of women with a high risk profile for endometrial cancer, based on a endometrial thickness of ≥ 5mm.[35, 37, 38]

Figure 2. Quality of included studies



Study quality

The results of the quality assessment are reported in Figure 2. Overall, study quality was good. The quality of the description of the setting and study period was rated as moderate; this was not described in three out of nine articles. Three articles included all women with postmenopausal bleeding, but performed histology only in patients with an increased endometrial thickness. All three articles explained that no further investigations were performed in women with an endometrial thickness less than five mm, because evidence suggests a very low probability of cancer below this threshold.[33, 34, 36]

Table 1. Study characteristics of included articles

First author, year	Patients	Exclusion criteria	N	N malignancy (%)	Age (years)	Study design	Outcome	Prediction model
Epstein 2002	PMP bleeding, ET ≥ 5mm	Doppler artefacts, incorrect processing	83	16 (19%)	Mean 66	Prospective cohort	Endometrial cancer	2 models: both combination patient history, TVS and Doppler
Randelz-hofer 2002	PMP bleeding	HRT/Tamoxifen use	321	95 (30%)	47-91 (median 68)	Prospective cohort	Endometrial cancer	1 model: TVS only
Bachmann 2003	PMP bleeding, unscheduled bleeding on HRT	-	428	19 (4.6%)	28-61 (median 54)	Prospective cohort	Endometrial cancer	4 models: patient history, patient history + US, patient history + hyst, patient history + TVS + hyst
Bruchim 2004	PMP bleeding	HRT use	95	9 (9.5%)	46-94 (mean 60)	Cohort*	Endometrial cancer	1 model: patient history + TVS
Opmeer 2006	PMP bleeding	History of hysterectomy, HRT use, recurrent bleeding, TVS not possible/ not performed	540	56 (10.3%)	37-91 (mean 62)	Prospective cohort	Endometrial cancer or precancer	2 models: patient characteristics and one combined model with patient characteristics and TVS
Opolskiene 2007	PMP bleeding, ET ≥4.5 mm	Fluid in cavity, absence of power Doppler signals, large myomas, no histologic diagnosis	120	30 (25%)	*	Prospective cohort	Endometrial cancer	Many models: TVS and Doppler
Burbos 2010	PMP bleeding	Asymptomatic women	3047	-	35-97 (median 59)	Prospective cohort	Endometrial cancer	1 model: patient history + TVS
Burbos 2011	PMP bleeding	History of hysterectomy, asymptomatic women	3548	201 (6%)	54-73	Prospective cohort	Endometrial cancer	1 model: patient history only
Opolskiene 2011	PMP bleeding, ET ≥4.5 mm	Absence of processed ultrasound images or reliable histologic diagnosis	261	63 (24%)	47-91 (median 67)	Prospective cohort	Endometrial cancer	4 models: one based on patient history, 1 patient history + TVS, 2 patient history + TVS + Doppler

PMP = postmenopausal
ET = endometrial thickness
CH = cohort study
Hyst = hysteroscopy (pos/neg)
TVS = transvaginal sonography
HRT = hormone replacement therapy

* not well described

Predictor variables

The nine included articles investigated 27 different possible prediction variables (Table 2). Age was tested in all nine articles, turned out to be statistically significant in multivariable analysis in six articles and was used in the prediction model in six articles. Endometrial thickness was tested in eight articles, statistically significant in multivariable analysis in eight articles and used in eight prediction models. Most important predictor variables in patient history were: age, body mass index (BMI), diabetes, frequency of bleeding, use of anticoagulants and HRT. Endometrial thickness, endometrial morphology and endometrial border were identified as significant grey-scale TVS variables. In the three articles studying the use of Doppler for predicting endometrial cancer, endometrial colour score and vascularity index were identified as the most important predictor variables.

Phases of model development

All articles selected in this review addressed the first phase of developing a prediction model: model derivation.[24] Of the nine articles on predicting endometrial cancer in women with PMB, eight had been internally validated but none of these models passed the external validation phase. We asked all six research-groups, which developed the nine different prediction models if their models are undergoing external validation and we received response from all six research-groups. The two prediction models of Opolskiene et al,[37, 38] are undergoing temporal validation (internal validation in a newly recruited patient group) and external validation in an international multicentre study by Valentin et al No results are available yet, since they are still recruiting patients for these studies. The two prediction models developed by Burbos et al[33, 34] were recently used in an article to compare the performance in internal validation of these models.[43] This group is working on external validation. Finally, we can report that the prediction model of Opmeer et al[36] is currently being externally validated in two cohorts: one cohort in three different hospitals in the Netherlands and one in Skåne University Hospital Malmö in collaboration with the group of Valentin et al, but this external validation is not published yet. There were no impact analysis studies, i.e. studies that showed that the prediction model indeed improved patient outcome or was cost-effective in clinical practice.

Performance of the prediction models

The performance of the eight articles that were internally validated their models is presented in Table 3.[31, 33-39] Calibration was described in one article.[39] The estimated

probability of cancer and the observed proportion of patients with endometrial cancer are mentioned in Randelzhofer et al[39] However, calibration is generally reported as a calibration plot. None of the studies reported on calibration in a calibration plot. Discrimination was studied in seven out of eight articles by calculating an AUC. The AUC varied from 0.66 to 0.92 for different prediction models, with the highest AUC for a model combining Doppler and grey-scale TVS.[37] In all internally validated studies clinical usefulness is described, with the highest sensitivity and the lowest negative LR for a combined model with patient characteristics, grey-scale TVS and Doppler.[38] The highest NPV found for a model was 0.996 for a model, which combined patient history, endometrial thickness and histology in a sequential strategy.[36] The performance of the four models using only patient characteristics showed a high sensitivity or high NPV in two models[36, 38] and a low LR for a negative outcome in one model.[38] All three studies in which Doppler was studied as a predictor variable, reported this information to contribute to the prediction of endometrial cancer in women with PMB.[35, 37, 38] Endometrial thickness was used as a variable in eight prediction models and seven found that incorporating endometrial thickness may improve diagnostic accuracy of a model.

Discussion

We systematically reviewed existing prediction models for endometrial cancer in women with PMB and to identify the most important predictor variables. We found nine studies reporting on the development of prediction models for endometrial cancer in women with PMB. Eight of these studies described at least one aspect of internal validation and until now, none of the prediction models have been externally validated.

The different predictor variables can roughly be divided into four subjects: patient characteristics, grey-scale ultrasound variables, Doppler ultrasound variables and hysteroscopy variables. Most prediction models used a combination of these subjects to predict the chance of endometrial cancer. We chose to limit our list of most important predictor variables to those, which had been considered as statistically significant input variables in three or more studies and to those, which were significant input variables in two studies and had not been tested in other studies. By doing this, we identified the most important variables, without missing possible important variables, which have not yet been extensively studied. Using

these limits we identified 11 important input variables for predicting endometrial cancer in women with PMB (Table 2).

Almost all articles reported performance in terms of discrimination and/or clinical usefulness, whereas calibration was reported only incidentally. In this study, we identified five articles describing a prediction model with good discrimination (AUC of >0.8).[31, 35-38] Because only one study described data on calibration, there is insufficient data available to draw conclusions on calibration.

Two studies showed best performance regarding discrimination and clinical usefulness: Opolskiene et al 2011 and Opmeer et al 2007. In the model by Opolskiene et al 2011, a combination of patient characteristics, grey-scale TVS and Doppler was used. They concluded that their model excludes endometrial cancer reasonably well when power Doppler is added. Furthermore, in all three studies that used Doppler, Doppler was found to contribute to the prediction of endometrial cancer in women with PMB.[35, 37, 38] Based on this, we could conclude that the best model in predicting endometrial cancer is a model, which uses a combination of patient characteristics, endometrial thickness and power Doppler. However, power Doppler cannot be used in all patients. All three Doppler-models excluded patients based on different reasons: Doppler artefacts, incorrect processing of TVS image, fluid in the cavity and absence of Doppler signals or large myomas. Another limitation in the use of power Doppler is that these studies do not give information on the interobserver variability and learning curve in measuring Doppler variables. For application of results found in Doppler studies, it is important to use the same ultrasound system, as the colour content of a power Doppler scan depends heavily on Doppler sensitivity.[38]

Although the performance of the models using Doppler seems reasonable, a model using patient characteristics and endometrial thickness might be more useful in daily practice. In a health care system with general practitioners referring patients with a high risk of malignant disease to a specialist, the best model would be a model that can distinguish women with a high risk of endometrial cancer from women with a low risk based on patient characteristics only. Such a model would also be useful in situations where TVS is not directly available. Only women with a high risk could be referred for TVS or to the gynaecologist for a further evaluation and women with a low risk could be reassured and referred only at recurrent bleeding. Based on this review we couldn't identify a model with a good performance in internal validation based on patient characteristics only. However, two of four models based on patient characteristics showed good performance in clinical usefulness with a high sensitivity, a high NPV and/or a low LR for a negative outcome.[36,38] Based on these results we

can conclude that although these models do not show a high AUC, they could be useful in clinical practice. These models were found to discriminate women with a high risk for endometrial cancer from women with low risk and to select women for further (invasive) testing.

The conclusions above are based on reported model performance based on internal validation only. To implement a prediction model into clinical practice, external validation is essential. McGinn et al describe three reasons.[25] A prediction model may reflect associations between given predictors and outcomes that are primarily due to chance. Secondly, the predictor variables used in a model may be idiosyncratic to that specific population, which suggests that the prediction model may fail in a new setting. And thirdly, clinicians may fail to implement the model comprehensively or accurately in their clinical practice. The result would be that a model succeeds in theory, but fails in practice. For a successful implementation, a model should be validated both internally and externally and finally go through the phase of impact analysis in the same population in which a model is derived. As none of the prediction models have completed the phase of external validation, they cannot be used in clinical practice yet.

When evaluating these prediction models by external validation or finally in impact analysis, one should keep in mind that these models were developed in different patient populations. The target population in which a model is derived should be the same as the population in which a model is tested or clinically used. Selecting a high-risk population (for example, a population with an ET ≥ 5mm) will result in a different performance and possibly in the selection of different predictor variables compared to an unselected population of women with PMB. Furthermore, in an unselected population there could be implicate selection dependent of a population within a general practice or a population within a gynaecological practice or differences in health systems in different countries. Different populations have different prevalence of endometrial cancer, which could be an explanation for the differences found in the performance of the models. A consensus has not been found in systematic reviews or in international guidelines regarding the best sequence of diagnostic procedures for women with PMB.[9] Considering the performance of the existing prediction models, we can conclude that we have indications that the first step in the approach of women with PMB should be to distinguish between women with low versus increased risk of having endometrial cancer and the next step would be to refer patients for TVS or further invasive testing.

Table 2. Predictor variables evaluated and used in the prediction models

	Epstein 2002	Randelzhofer 2002	Bachmann 2003	Bruchim 2004	Opmeer 2006	Opolskiene 2007	Burbos 2010	Burbos 2011	Opolskiene 2011
Patient history variables									
Age	3	2	1	1	1	2	1	1	1
BMI					1		1	1	3
Diabetes			3		1		1	1	3
Frequency of bleeding							1	1	
Amount of bleeding							3	3	
HRT use	1		1			3	3	3	1
Anticoagulant use					1				1
Nulliparity					1				3
Time since menopause	3			2					
VAS-score									1
Examiner	3								
Hypertension			3		2		2	2	3
Thyroid dysfunction					3				3
History of cancer					3		2	2	
Ultrasound variables – grey-scale									
Endometrial thickness	1	1	1	1	1	1	1		1
Heterogeneous echogenicity/morphology	1	1				1			
Endometrial border		1				1			
Endometrial fluid in cavity		3							
Endometrial area	2								
Ultrasound variables – Doppler									
Vascularised area	2					1			
Endometrial colour score	1								1
Irregular branching						1			
Vascularity index	1								1
Mean intensity of pixels in endometrial area	2								
Mean intensity of pixels in vascularised area	3								
Hysteroscopy variables									
Suspicious hysteroscopy findings			1						

1 = statistically significant in multivariate analysis and included in model
2 = statistically significant in univariate analysis and not included in model
3 = not statistically significant and not included in prediction model

Table 3. Evaluation of model development and model performance

			Specification of model performance at internal validation			
First author, year	**Development phase**	**Prediction model**	**Discrimination#**	**Calibration**	**Clinical usefulness**	**Result as reported in paper**
Epstein 2002	Internal validation	Subjective prob of cancer (PH, TVS, Doppler) Objective prob of cancer (PH, TVS, Doppler)	0.88 0.88	- -	Sens 0.75, Spec 0.96 Sens 0.88, Spec 0.81	Power Doppler can contribute to diagnosis of endometrial cancer.
Randelzhofer 2002	Internal validation	ET+endometrial structure + myometrial border (cut-off point ET>10mm)	-	Estimated prob 2.8% vs. 2.1% real malignant	Sens 0.97, Spec 0.62 NPV 0.98, Accuracy 0,72	The combined assessment of ET and endometrial morphology may improve diagnostic accuracy.
Bachmann 2003	Internal validation	PH PH+ET PH+hysteroscopy PH+ET+hysterscopy	0.8 0.82 0.910 0.914	-	-	Not much increased value in testing with ultrasound, if hysteroscopy was already performed.
Bruchim 2004	Model derivation	ET+time since menopause	-	-	-	Time since menopause and ET can define when invasive testing is needed.
Opmeer 2006	Internal validation	PH PH+TVS if prob>4% PH+TVS, histology if prob >4%	0.76 0.76 0.9	-	NPV 0.990 Efficiency +0.6 NPV 0.990 Efficiency -0.16 NPV 0.996 Efficiency -0.05	Compared with US only, efficiency gain is reflected in increased AUC and reduced number of procedures, with PH+US in a sequential strategy.
Opolskiene 2007*	Internal validation	ET, echogenicity (and Doppler)	0.91 / 0.92	-	Sens 0.93/0.87 Spec 0.79/0.83 LR- 0.1 / 0.2	A model including ET and heterogeneous echogenicity of the endometrium was best in predicting endometrial cancer, with Doppler diagnostic performance improved marginally
Burbos 2010	Internal validation	DEFAB: diabetes, ET, frequency of bleeding, age and BMI (DEFAB ≥3)	0.77 / 0.66	-	Sens 0.82 Spec 0.50 Accuracy 0.52 LR- 0.36	Fair accuracy in separating women without cancer from women with cancer.

Table 3. Continued

			Specification of model performance at internal validation			
First author, year	**Development phase**	**Prediction model**	**Discrimination#**	**Calibration**	**Clinical usefulness**	**Result as reported in paper**
Burbos 2011	Internal validation	FAD 31: frequency of bleeding, age, diabetes, BMI cut-off 31 (cut-off FAD 31 ≥4)	0.73 / 0.66	-	Sens 0.80 Spec 0.51 Accuracy 0.53 LR- 0.39	Reasonable discriminatory ability.
Opolskiene 2011	Internal validation	PH PH+ET PH+ET+Doppler(VAS) PH+ET+Doppler(VI)	0.74 0.82 0.89 0.91	- - - -	Sens 0.89, LR- 0.22 Sens 0.84, LR- 0.24 Sens 0.70, LR- 0.31 Sens 0.89, LR- 0.14	Fairly good in excluding endometrial cancer when power Doppler is added.

Prob = probability; PH= patient history;
TVS= transvaginal ultrasound; ET = endometrial thickness

* as many models are described we selected the model with the best performance
# discrimination is reported as AUC of the ROC curve

Future perspective

The prediction models that have been developed for women with postmenopausal bleeding showed good performance but have only reached the phase of internal validation. Future research should focus on external validation and impact analysis of these prediction models. We hope that these will confirm their prognostic abilities, so that in the next few years, prediction models can be implemented in general gynaecological practice. Based on this review, we conclude that clinical prediction models show promising results, but further external validation is required as well as impact analysis to maximise diagnostic accuracy of the models at an acceptable patient burden and for acceptable health care costs.

Appendix 1

Search strategy – MEDLINE

#	Searches
1.	postmenopause [mesh]
2.	postmenopau* [tw]
3.	post-menopau* [tw]
4.	#1 OR #2 OR #3
5.	hemorrhage [tw]
6.	bleed* [tw]
7.	hemorrhag* [tw]
8.	haemorrhag* [tw]
9.	blood loss* [tw]
10.	#5 OR #6 OR #7 OR #8 OR #9
11.	endometrial neoplasms [mesh]
12.	endometrial neoplasm* [tw]
13.	endometrial cancer* [tw]
14.	endometrial cancer* [tw]
15.	endometrial malignanc* [tw]
16.	endometrial tumo* [tw]
17.	corpus uteri cancer* [tw]
18.	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
19.	endometrial hyperplasia [mesh]
20.	endometrial hyperplasia* [tw]
21.	#19 OR #20
22.	#18 OR #21
23.	predict* [tiab]
24.	clinical* [tiab]
25.	outcome* [tiab]
26.	risk* [tiab]
27.	#23 OR #24 OR #25 OR #26
28.	#4 AND #10 AND #22 AND #27

Search strategy – EMBASE

#	Searches
1.	postmenopause/
2.	(postmenopau* or post-menopau*).tw.
3.	(after menopaus* or after the menopaus* or following menopaus* or following the menopaus*).tw.
4.	or/1-3
5.	exp bleeding/
6.	(bleed* or hemorrhag* or haemorrhag* or blood loss*).tw.
7.	or/5-6
8.	endometrial neoplasms/
9.	endometrial neoplasm* or endometrial cancer* or endometrial cancer* or endometrial malignanc* or endometrial tumo* or corpus uteri cancer*).tw
10.	or/8-9
11.	endometrial hyperplasia/
12.	endometrial hyperplasia.tw.
13.	or/11-12
14.	10 or 13
15.	(predict* or clinical* or outcome* or risk*).ti,ab.
16.	4 and 7 and 14 and 15

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Chapter 4

External validation of a mathematical model to estimate the probability of endometrial cancer of women with postmenopausal bleeding

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Submitted

Abstract

Objective To externally validate two previously developed prediction models that estimate the probability of endometrial cancer in women with postmenopausal bleeding.

Design and setting We performed an external validation study of two previously developed prediction models in two independent datasets of consecutive women not using hormone replacement therapy with a first episode of postmenopausal bleeding.

Population We studied women with postmenopausal bleeding. One dataset (559 women) was prospectively collected in three general hospitals in the Netherlands including, the other dataset (433 women) was prospectively collected in a university hospital in Sweden.

Methods We retrospectively evaluated two models that predict endometrial cancer in the two validation databases. We then evaluated three diagnostic strategies, a 'patient characteristics' rule, based on characteristics of the women without transvaginal ultrasound, a 'sequential' rule, i.e. ultrasound in case the probability for cancer exceeded 4% based on characteristics, and subsequent histological analyses when the endometrial thickness exceeded 4 mm and an 'integrated' rule with a probability estimate based on both characteristics of the women and ultrasound results and endometrial sampling when the probability of cancer exceeded 4%.

Main outcome measures We studied the performance of the models in terms of discrimination and calibration. We then calculated the number of carcinomas detected and missed using the three different strategies, as well as the number of ultrasounds and invasive procedures performed with the three different strategies.

Results In both the Dutch and the Swedish databases, the two models showed good performance in terms of discrimination and calibration. The three strategies, based on these two models, all detected all women with endometrial (pre) cancer. Applying the 'integrated' or 'sequential' strategy would, compared to current practice (ultrasound only), leads to a 3 to 6 % decrease in the number of women in need for further invasive testing.

Conclusions We found that two models for endometrial cancer maintained their diagnostic performance in two independent validation databases. The use of a 'patient characteristic and ultrasound' model in a sequential or integrated strategy, could slightly reduce the number of invasive procedures without loss in detection of endometrial cancer.

Introduction

Postmenopausal bleeding (PMB) is a common complaint in postmenopausal women and in about 10% of women endometrial cancer is the underlying cause of PMB.[1]

In the 1990s endometrial thickness measurement with transvaginal ultrasonography (TVS) was introduced as a test to distinguish between women with a low and a high risk of endometrial cancer.[2] The cut-off point for a thin endometrium, and thus a low risk of endometrial cancer, varies in different guidelines between three and five millimetres.[3] Patients with a thin endometrium can be reassured as their post-test probability of endometrial cancer is lower than one per cent, which is a worldwide-accepted threshold for patient reassurance.[1,4,5] The post-test probability depends not only on the endometrial thickness, but also on the pre-test probability, which depends on patient's characteristics. In women with PMB, characteristics that define the pre-test probability of endometrial cancer are: age, time since menopause, body mass index (BMI), hypertension, diabetes mellitus, anticoagulants use and parity.[6-12]

Several studies have described the prevalence of these characteristics and developed different prediction models to estimate the individual chance of having endometrial cancer[13]. However, none of the existing prediction models have yet been externally validated, which is necessary for successful implementation[14]. All models were internally validated in their development database and two models showed the best performance.[15,16] Opolskiene et al concluded that their model excludes endometrial cancer reasonably well when power Doppler is added, but because Doppler is not commonly used in daily practice, we decided to validate two multivariable models without Doppler, described by Opmeer et al[15,16] These two models had been internally validated in their development database.[13]

The aim of the present study was to externally validate the diagnostic performance of these two models and estimate the clinical consequences of the three management strategies suggested in this article by retrospectively applying the models on two independently prospectively collected databases of women with PMB.

Methods

The multivariable models and management strategies

Opmeer et al developed two multivariable logistic regression models for the

prediction of endometrial cancer in women with postmenopausal bleeding based on the following patient characteristics: age, time since menopause, body mass index (BMI), diabetes, parity, hypertension, use of anticoagulants, history of cancer and dysfunction of the thyroid gland. The first statistical model, based on characteristics of the women only, is referred to as the 'patient characteristics model'. The second model is an extension of the first model in which characteristics of the women are combined with the measurement of endometrial thickness by TVS and is referred to as the 'patient characteristics and TVS model'. Further statistical details on the development of the model can be found in the Appendix of the original article.[16]

Study population used for external validation

The two models and three strategies were externally validated by retrospectively applying them on two prospectively collected databases:

- Dutch database: This database studying 559 women included all women presenting with postmenopausal bleeding between January 2009 and April 2011 (36% of women presented at the TweeSteden Hospital, 18% at the Maxima Medical Centre in Veldhoven and 46% at the St. Antonius Hospital in Nieuwegein, the Netherlands). This database was not primarily established to validate the two mathematical models of Opmeer et al Menopause was defined as at least one year of amenorrhea, after the age of forty. If there were doubts about menopausal status the status was established by testing of the follicle-stimulating hormone (FSH). The following patient characteristics were recorded: age, years since menopause, BMI, parity, HRT use, hypertension, diabetes, use of anticoagulants and endometrial thickness as measured by TVS. If endometrial thickness exceeded four millimetres, endometrial sampling using the Pipelle® (Labaratoire CCD, Paris, France) was performed. In case of a failed endometrial sampling hysteroscopy with directed biopsy was performed. Failure was classified as either a technical failure or as an endometrial sampling in which the amount of tissue was insufficient for a reliable diagnosis. All women were instructed to contact the hospital if recurrence of bleeding occurred.

- Swedish database: This database includes all women presenting with PMB at the Skåne University Hospital in Malmö postmenopausal bleeding clinic

between November 2002 and June 2009. Menopause was defined as at least one year of amenorrhea after the age of 40. The following patient characteristics were recorded: age, age at menopause, weight, height, parity, HRT use, hypertension, diabetes, use of anticoagulants and endometrial thickness measured by TVS. If endometrial thickness exceeded 4.4 mm, saline infused sonography (SIS) was performed. If there were no focal lesions in the uterine cavity at SIS, an endometrial sample using the Endorette® (Medscan AB, Malmö, Sweden) was taken. If there were focal lesions at SIS or if SIS failed, hysteroscopy with resection of focal lesions (if present) and supplementary dilatation and curettage were performed.[15] Women in whom endometrial sampling was not performed because of endometrium $\leq$ 4.4 mm were instructed to contact the hospital if recurrence of bleeding occurred.

Follow-up in the Dutch database was based on data collected from case notes. For the purpose of this study, all women with an endometrial thickness below the cut-off value, who did not have endometrial sampling without recurrent bleeding, were considered negative for endometrial cancer. In case of recurrent bleeding, hysteroscopy was performed. The median follow-up time in this database was 26 months (range 18 to 43 months).

In the Swedish database, all women with an endometrial thickness $\leq$ 4.4 mm (and therefore without a histological diagnosis of the endometrium) were matched with the regional cancer register to ascertain that none of these women were diagnosed with endometrial cancer after inclusion in the study. Indeed, no woman with endometrial thickness $\leq$ 4.4 mm was found to have endometrial cancer and all were classified as not having endometrial cancer.

Women were excluded from our statistical analysis if the endometrial thickness was not measurable. The Swedish database does not include women with fluid in the uterine cavity. Precancer, defined as any form of hyperplasia with atypia, and cancer in the histology specimen were classified as 'endometrial cancer'. All other histological diagnoses were classified as benign.

Statistical analysis of patient characteristics

We compared patient characteristics between the two databases with the chi-square test. Continuous variables were tested for normal distribution, and the independent

T-test or Mann–Whitney U-test for univariate analysis was used to compare means or medians. For analysis, the Statistical Package for the Social Sciences (IBM Corp, Armonk, NY, USA) version 20.0 was utilized. Statistical significance was set at $p < 0.05$.

Imputation of missing values

In our validation study, we performed multiple imputations for missing data elements, with separate imputation rounds for each of the two databases. In multiple imputation, each missing value is imputed several times. The variation among the imputations reflects the uncertainty with which the missing values can be predicted from the observed ones. After combining the results, the pooled estimates and standard errors reflect missing data uncertainty.[17-19]

External validation

We retrospectively applied the two models developed by Opmeer (patient characteristics only, patient characteristics and TVS) to the women in the Dutch and Swedish databases. We assessed the performance of the models by examining calibration (agreement between predicted risks and observed frequencies of endometrial cancer) and discriminative performance (the ability of the models to distinguish between women with and without endometrial cancer). To assess calibration for the two models, we plotted the predicted probabilities of endometrial cancer and the observed proportion of endometrial cancer by deciles of the predicted probabilities in a calibration plot.[20] Calibration is considered perfect if the intercept is 0 and the calibration slope is 1).[21,22] Calibration is relevant to evaluate the accuracy of the risk estimates provided by the models (do patients with predicted risk of 25% indeed have a risk of 1 in 4 of having endometrial cancer), but in clinical practice high performance in terms of identified and missed cases at a certain threshold will be required. Calibration analyses were performed using R version 15.2.1.

Discriminative performance of the two models was assessed by calculating the area under the receiver operator characteristic curve (AUC). AUCs reflect the overall discriminative taking into account the full spectrum of predicted probabilities. As such, they are informative from a statistical perspective, but a model with lower AUC may show superior clinical performance at a particular threshold as compared to a model with higher AUC.

Based on these two statistical models, three different diagnostic strategies were explored:

1. The 'patient characteristics' rule, i.e. probability estimates based on characteristics of the women, and invasive diagnostics in case the probability of (pre)cancer exceeded 4%. In this rule, TVS was not performed.
2. The 'sequential' rule, i.e. probability estimates based on characteristics of the women, with TVS in case the probability for cancer exceeded 4%, and subsequent histological analyses when the endometrial thickness exceeds 4 mm.
3. The 'integrated' rule, i.e. TVS in all women, with a probability estimate based on both characteristics of the women and TVS results, completed by endometrial sampling when the probability of cancer exceeded 4%.

To estimate the clinical consequences of applying these three different management strategies proposed by Opmeer et al on the validation datasets,[16] we calculated for each of the three strategies, the percentage of women in whom TVS would be performed, the percentage of women in whom an invasive procedure would be performed to obtain material for histology, the number of endometrial (pre) cancers identified by the different strategies and specificity (the amount of patients without cancer who fell below the threshold of the specific strategy). We compared all these clinical consequences with the current strategy used in clinical practice: selecting women for further diagnostic work-up by the measurement of endometrial thickness (TVS only). We performed all analyses for the external validation in 'R', version 2.15.0 (2012).

Results

Patient characteristics

The two databases available for external validation consisted of 559 Dutch and 433 Swedish women with PMB not using HRT. Table 1 shows the characteristics of women in the two databases and the percentage of missing data per database. Age, time since menopause, anticoagulants use, body mass index (BMI), endometrial thickness and the prevalence of endometrial cancer differed significantly between the two validation populations, women in the Swedish database being older, having

lower BMI, thicker endometrium, a higher percentage of endometrial cancer and more Swedish women used anticoagulant therapy. For both validation databases, efforts were made to collect data on endometrial cancer in the women with an endometrial thickness below the applied threshold and in none of these women endometrial cancer was diagnosed.

Table 1. Patient characteristics and missing values in validation databases

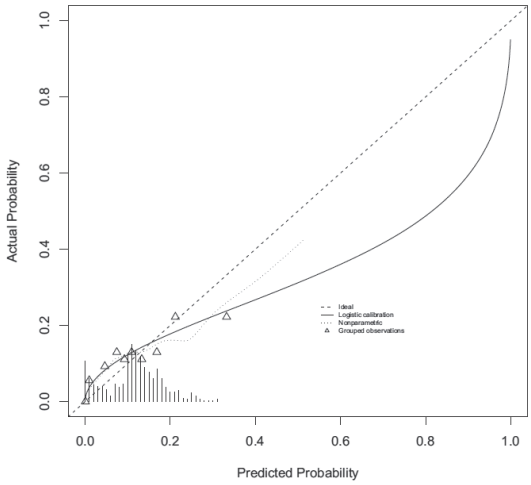
	Swedish database	Missing; n (%)	Dutch database	Missing; n (%)	p-value
N	433		559		
Age, years; mean (SD)	67.4 +/- 11.8	0	61.8 +/- 9.95	0	<0.01
Diabetes mellitus; n (%)	66 (15.2)	0	72 (12.9)	1 (0.2)	0.29
Hypertension; n (%)	176 (40.6)	0	196 (35.1)	0	0.07
Anticoagulants; n (%)	88 (31.9)	157 (13.2)	94 (16.8)	0	<0.01
BMI, kg/m^2; mean (SD)	27.8 (6.4)	24 (5.5)	30.2 (8.2)	260 (43.4)	<0.01
Time since menopause, years; median (IQR)	16 (5-26)	6 (1.4)	5 (2-14)	124 (22.2)	<0.01
Nulliparity; n (%)	45 (10.6)	8 (1.8)	60 (13.5)	114 (20.4)	0.19
Endometrial thickness, mm; median (IQR)	6.0 (3.2-13.0)	0	5.7 (2.5-10.0)	0	0.02
Endometrial (pre-) cancer; n (%)	65 (15.0)	0	57 (10.2)	0	0.02
Atypical hyperplasia	3 (0.69)		7 (1.3)		
Endometrial cancer	62 (14.3)		50 (8.9)		

BMI, body mass index; NA, not applicable.

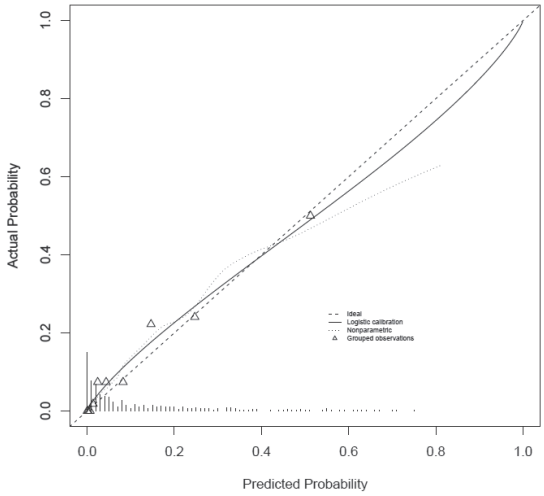
Calibration

Plots that express the calibration of the two models developed by Opmeer ('patient characteristics' model and the 'patient characteristics and TVS' model) in the Dutch and Swedish database are presented in Figure 1. In the Dutch database, the calibration slope was better for the 'patient characteristics and TVS' model than for the 'patient characteristics' model. The predicted probabilities of cancer when using the 'patient characteristics and TVS' model were close to the observed frequency of cancer over the whole range of predicted risks. For the lowest risk group, calibration was consistently good across the different models and databases, and some major over and underestimated risk in patients at increased risk for endometrial cancer.

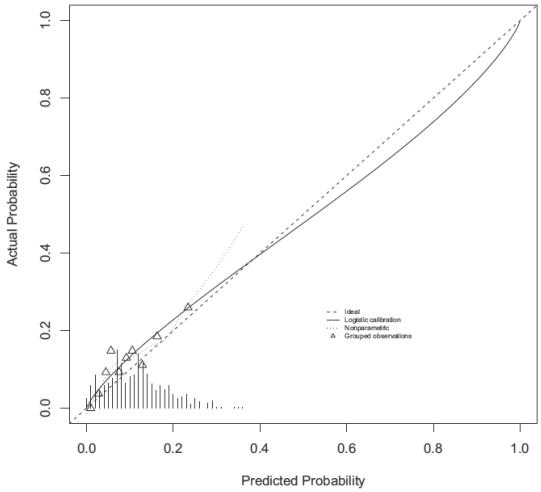
Figure 1. Calibration plots for the two prediction models



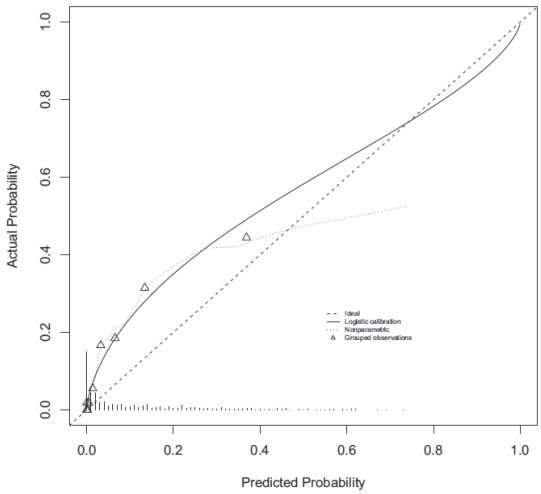
A. 'Patient Characteristics' model Dutch validation database



B. 'Patient Characteristics and TVS' model Dutch validation database



C. 'Patient Characteristics'-model Swedish validation database



D. 'Patient Characteristics and TVS'-model Swedish validation database

In the Swedish database, the calibration slope performed better for the 'patient characteristics' model than for the 'patient characteristics and TVS' model. For the 'patient characteristics' model, predicted probabilities were close to the observed frequency over the whole range of predicted risks. The 'patient characteristics and TVS' model underestimated the probability of endometrial cancer over almost the whole range of probabilities.

Discriminative performance of the prediction models

Figure 2 shows ROC curves for the two models compared to endometrial thickness as measured by TVS in the two validation datasets. In both the Dutch and the Swedish databases, the AUC for the 'patient characteristics and TVS' model (respectively 0.89 (95% CI 0.86 to 0.92) and 0.89 (95% CI 0.86 to 0.91)) was higher than the AUC for the 'patients characteristics' model (0.71 (95% CI 0.65 to 0.76) and 0.69 (95% CI 0.64 to 0.73)). The AUC for the 'patient characteristics and TVS' model was similar to the AUC for endometrial thickness only: 0.87 (95% CI 0.83 to 0.90) in the Dutch database and 0.90 (95% CI 0.88 to 0.93) in the Swedish database.

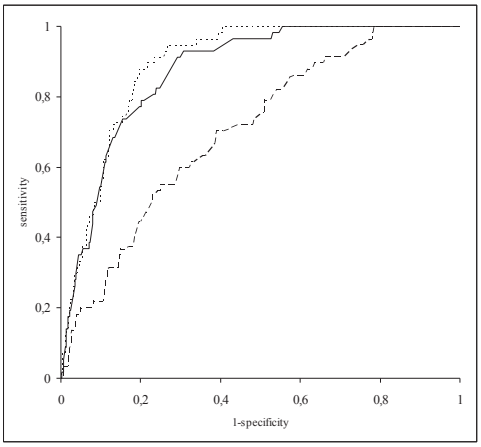
Clinical consequence of the three strategies

The estimated clinical consequences of applying the three strategies are reported in Tables 2 and 3. With all three strategies, all cases of endometrial (pre) cancers would be detected in both databases. This is under the assumption that among women with a thin endometrium (below the threshold of 4 or 4.4 mm) was diagnosed with endometrial cancer. This means that with the 'patient characteristics' strategy you could skip the measurement of endometrial thickness safely, but then you would have to perform an invasive procedure to get histology in 93% of women in both databases, compared to only 61-63% (respectively in the Dutch and Swedish database) when patients would be selected based on the measurement of endometrial thickness (which is current clinical practice).

When using the patient characteristics in a 'sequential' strategy, one could save 7% of women an ultrasound and these could be reassured. In the remaining group of women endometrial thickness has to be measured and then 57-58% would have to undergo an invasive procedure. Thus, this strategy would save 7% of women an ultrasound and in 3-6 % less women an invasive procedure has to be done compared to the current clinical practice: TVS only.

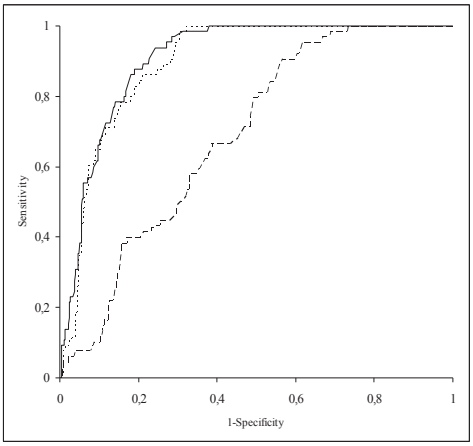
When using the patient characteristics in an 'integrated' strategy, all women would need a TVS and the amount of women that would need further invasive procedures to retrieve histology would be the same as in the 'sequential' strategy.

Figure 2. ROC curves 'Patient Characteristics only'-model and 'Patient Characteristics and TVS'-model.



A. Dutch validation database

_ _ 'Patient characteristics'-model, AUC: 0.71 (95% CI: 0.65 to 0.76)
_ _ _ 'Patient characteristics and TVS'-model, AUC: 0.89 (95% CI: 0.86 to 0.92)
____ TVS only, AUC: 0.87 (95% CI: 0.83 to 0.90)



B. Swedish validation database

_ _ 'Patient characteristics'-model, AUC: 0.69 (95% CI: 0.64 to 0.73)
_ _ _ 'Patient characteristics and TVS'-model, AUC: 0.89 (95% CI: 0.86 to 0.91)
____ TVS only, AUC: 0.90 (95% CI: 0.88 to 0.93)

Table 2. Clinical consequences of strategies, Dutch database

Decision strategy	Description	TVS N (%)	Invasive procedures N (%)	(Pre) cancers detected N (%)	Specificity
Reference strategy	TVS only (current practice) > 4mm	559 (100%)	352 (63.0%)	57 (100%)	0.41
'Patient characteristics' strategy	Histological analysis if probability based on characteristics of the women exceeds 4% (no TVS)	0 (no TVS)	521 (93.2%)	57 (100%)	0.08
'Sequential' strategy	Decision for TVS based on probability of cancer calculated from characteristics of the women, TVS only performed when probability exceeds 4%, histological analysis if TVS > 4mm	521 (93%)	320 (57.2%)	57 (100%)	0.48
'Integrated' strategy	TVS in all women, decision for histological analysis if probability for endometrial cancer calculated from characteristics of the women and TVS model exceeds 4%	559 (100%)	316 (56.5%)	57 (100%)	0.48

Table 3. Clinical consequences of strategies, Swedish database

Decision strategy	Description	TVS N (%)	Invasive procedures N (%)	(Pre) cancers detected N (%)	Specificity
Reference strategy	TVS only (current practice) > 4mm	433 (100%)	265 (61.2%)	65 (100%)	0.46
'Patient characteristics' strategy	Histological analysis if probability based on characteristics of the women exceeds 4% (no TVS)	0 (no TVS)	401 (92.6%)	65 (100%)	0.09
'Sequential' strategy	Decision for TVS based on probability of cancer calculated from characteristics of the women, TVS only performed when probability exceeds 4%, histological analysis if TVS > 4mm	401 (92.6%)	251 (58.0%)	65 (100%)	0.49
'integrated' strategy	TVS in all women, decision for histological analysis if probability for endometrial cancer calculated from characteristics of the women and TVS model exceeds 4%	433 (100%)	248 (57.2%)	65 (100%)	0.50

Discussion

In this external validation study, we demonstrate that the diagnostic performance (i.e. Discrimination and calibration) in external validation of the two models is similar to the discriminative performance of the models in internal validation in the development database.[16] The model with the best discriminative performance in this external validation is the patient 'characteristics and TVS' model. However, we found that the discriminative performance of the 'patient characteristics and TVS' model is similar to that of endometrial thickness measurements with TVS (TVS-only), i.e. adding clinical information to endometrial thickness measurement does not significantly improve the ability to discriminate between benign and malignant endometrium.

Applying a strategy basing the decision to perform further invasive diagnostics on an individual risk calculated with 'patient characteristics only' would be safe. This means, no endometrial (pre) cancer that would have been detected by selecting women with TVS would be missed if these women would be selected based on patient characteristics only. However, you would need to perform invasive diagnostics in 93% of women, compared to only 61-63% (respectively in the Dutch and Swedish database) when patients would be selected based on TVS.

An important strength of our study is the external validation of the models using data from a different region within the Netherlands as well as data from another European country. External validation, assessing the validity and generalizability of a model is an essential step before a model can be implemented in practice.[21,23] To our knowledge this is the first study to describe external validation of a prediction model estimating the risk of endometrial cancer in women with PMB. As the TweeSteden Hospital also participated in the development study of the two prediction models by Opmeer et al, the population used for external validation has a minor overlap with the development population, yet with completely separate samples (different women in the development and validation sample).

As many data were collected as part of clinical practice, not all information was available for all women. Multiple imputation was used to deal with these missing data. Multiple imputation, even with a relatively large amount of missing data, gives a more precise and valid measure of association for variables with missing values than complete case analysis.[17,21] Generally, dropping cases with missing values (complete case analysis) yields biased results, and the discriminative ability of a multivariable model is reduced when cases with missing values are excluded from analysis.[21]

Another limitation is the fact that partial verification was performed in both databases. In women with an endometrial thickness below the applied threshold no histological assessment was performed. This is in agreement with clinical policy since more than 15 years in both Sweden and the Netherlands, and for practical and ethical reasons we have not included this assessment for research purposes only. For both validation databases however, efforts were made to collect information on these women by assessing patient charts and in the Swedish database matching the patients with the regional cancer registry. Evidently, there remains some uncertainty whether indeed no endometrial cancers were missed in this group, but with our approach we minimised this risk by our follow-up efforts.

Several prediction models have been published to estimate the risk of endometrial cancer in women with postmenopausal bleeding.[13] Opolskiene et al developed four prediction models including clinical and ultrasound information for women with endometrial thickness ≥ 4.5 mm. The first model is based on patient characteristics and in the development database an AUC of 0.74 was found. The second model is based on patient characteristics and endometrial thickness as measured with TVS, with an AUC of 0.82. The last two models are based on patient characteristics combined with sonographic endometrial thickness and two different Doppler characteristics, with AUC of 0.89 and 0.91 respectively. The authors concluded that the models are fairly good in excluding endometrial cancer when power Doppler is added.[15] Burbos et al developed two models based on patient characteristics with (AUC 0.77) and without endometrial thickness (AUC 0.73).[24] The authors concluded that the model based on patient characteristics has a reasonable discriminatory ability and the model based on patient characteristics and endometrial thickness has a fair accuracy in separating women without cancer from women with cancer. These findings are similar to the findings of internal validation of the models by Opmeer et al[16] None of these models have yet been externally validated.[13]

Before a prediction model can be implemented in clinical practice, external validation is essential.[14] In this external validation we found that the 'patient characteristics and TVS' model shows good discriminative performance (AUC) and a reasonable performance on calibration, however it is comparable to the use of TVS-only. All three strategies based on the 'patient characteristics and TVS' model could be safely implemented in daily practice, i.e. without missing any additional (pre) cancers compared to TVS-only, which is the current daily practice. To choose which strategy is used best in clinical practice, one could focus on the availability and use of different diagnostic tests. In situations were no ultrasound is available, women

could be selected based on their characteristics, however with a very low specificity which means that many women need to undergo further invasive testing with a small chance of diagnosing a (pre) cancer.

This study shows that after external validation in two independent datasets, the two multivariable models maintain their diagnostic performance and are able to select women with PMB not using HRT with a low risk of having endometrial cancer. By using the 'patient characteristic and TVS' model in a sequential or integrated strategy, the number of women that need further invasive procedures to obtain material for histological assessment can be decreased only a little, compared to the current diagnostic pathway in which patient characteristics are not taken into account. Therefore we think that these models are moderately useful in current daily practice. In the Netherlands, TVS is easy accessible in daily practice. A model based on patient characteristics would only be useful if a larger amount of invasive procedures could be decreased. Future research should focus on adjusting the model with different thresholds or subgroups of patients. Furthermore, as Doppler will be used more and more in clinical practice it would be worth it to externally validate a model which uses Doppler features.

Conclusions

The two models for endometrial cancer based on patient characteristics and TVS, maintained their diagnostic performance in two independent validation databases. The use of a 'patient characteristic and TVS' model in a sequential or integrated strategy, could slightly reduce the number of invasive procedures, compared to the current diagnostic pathway in which patient characteristics are not taken into account, without loss in detection of endometrial cancer. The 'patient characteristics' model is able to select women with a low risk of endometrial cancer, who can be reassured without further testing. This is especially useful in a setting where TVS is not (directly) available.

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Chapter 5

Diagnostic work-up for postmenopausal bleeding: a randomised controlled trial

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** contributed equally*

Submitted

Abstract

Objective To evaluate the effectiveness of hysteroscopic treatment of endometrial polyps versus expectant management in women with postmenopausal bleeding (PMB), a thickened endometrium and benign endometrial sampling.

Design Multicentre, randomised controlled trial.

Setting Three academic hospitals and nine non-academic teaching hospitals in the Netherlands.

Population Women with postmenopausal bleeding, an endometrial thickness > 4 mm and benign result of endometrial sampling.

Methods We randomised women for diagnostic work-up by hysteroscopy (preceded by saline infusion sonography) versus expectant management.

Main outcomes Primary outcome measure was the recurrence of PMB within a year after randomisation. Secondary outcome measures were time to recurrent bleeding and recurrent bleeding after more than one year. In the hysteroscopy group, the presence of polyps and the results of their histology were registered.

Results Between January 2010 and October 2013, we randomised 200 women, 98 to hysteroscopy and 102 to expectant management. Within one year a total of 15 women (15.3%) in the hysteroscopy group experienced recurrent bleeding, versus 18 (18.0%) in the expectant management group (relative risk 0.85 (95% CI 0.46-1.59). In the hysteroscopy group, we found 50 (51%) polyps at initial hysteroscopy. In the 50 polyps, the pathology results showed six (pre) cancers (6%).

Conclusion In women with PMB, a thickened endometrium and benign endometrial sampling, operative hysteroscopy does not reduce recurrent bleeding. Hysteroscopy detected focal endometrial (pre)cancer in 6% of women, who had benign endometrial sampling. This finding indicates that in these women, further diagnostic work-up is warranted to detect focal (pre)cancers, missed by endometrial sampling.

Trial registration Dutch trial register number NTR2130.

Introduction

Postmenopausal bleeding (PMB) is a common symptom in gynaecological practice[1]. It signals endometrial cancer in about 10% of the women.[2,3]

Guidelines on PMB emphasise the importance to diagnose or rule out endometrial cancer. Transvaginal sonography is used to distinguish between women with a low- or high risk for endometrial cancer. If the endometrium is thickened, endometrial sampling is performed to evaluate for endometrial cancer.[4-7]

When endometrial sampling shows a benign result, it is uncertain whether the work-up should be continued to detect benign intracavitary pathology. When women present with recurrent or persistent bleeding, further evaluation for focal lesions is required.[8-10] When a woman does not have persistent bleeding, guidelines leave room for individual patients and doctors to choose for expectant management or further diagnostic work-up,[8-10] since strong evidence on the effectiveness of polypectomy on the chance of recurrent bleeding is lacking. SIS and hysteroscopy are potentially helpful in the detection and removal of endometrial polyps.[11,12] However, hysteroscopy, despite being safe, well tolerated and performed in an outpatient setting, remains an invasive procedure with a potential risk of complications and at considerable cost.[11]

In case endometrial polyps remain undetected, they are believed to be responsible for recurrent vaginal bleeding.[13] Although polypectomy is one of the most performed hysteroscopic operations, only one cohort study is available, showing no difference in recurrent bleeding after hysteroscopy versus expectant management.[14]

In view of this lack of knowledge, we performed a multicentre randomised controlled trial in which we investigated the effectiveness of diagnostic work-up with hysteroscopy and subsequent polypectomy versus expectant management in women with PMB and benign endometrial biopsy. Since we performed SIS preceding the hysteroscopy, we were able to evaluate whether a strategy with SIS as triage for hysteroscopy would be effective.

Methods

Between January 2010 and October 2013, we performed a multicentre, randomised clinical trial in three academic and nine non-academic teaching hospitals. The trial was performed within the Dutch Consortium for research in Women's Health, a

collaboration of teaching and non-teaching hospitals in the Netherlands.[15] The study was performed by gynaecologists, registrars and research nurses. Full details about the trial protocol can be found at www.studies-obsgyn.nl/upload/protocol_pompoen 230908.doc. The trial was registered at the Dutch trial register (NTR2130). Approval for this study was obtained from the Medical Ethical Committee of the Academic Medical Centre, Amsterdam (MEC 2008-177) and from the Central Committee on Research involving Human Subjects (CCMO), The Netherlands. The local board of each participating hospital approved the study.

Participants

We studied women with PMB, defined as blood loss occurring after at least one year of amenorrhea above the age of 50. Hospitals participating in the study had a protocolled work-up for these women, based on the Dutch national guideline.[8] First, women underwent transvaginal sonography (TVS). The thickness of the endometrium was measured in the sagittal plane, including both layers of endometrium. All measurements were done with callipers on a frozen ultrasound image. In case the endometrial thickness was four millimetres or less, the patient was reassured, managed expectantly and advised to come back with recurrent bleeding. If the double endometrium thickness was more than four millimetres or not measurable, endometrial sampling was performed, using Pipelle® (Pipelle de Cornier, Paris, France), an office endometrial sampling device that is generally used in the Netherlands. In case the sampling device could not pass the cervical os, or the sampling result was inconclusive, the woman was scheduled for direct hysteroscopy and could not be included in this study.

Inclusion criteria were PMB, an endometrial thickness more than four millimetres and benign histology. The local pathologist examined the endometrial samples. We defined benign histology of endometrial sampling as the presence of benign endometrial stroma in the histology sample. Hyperplasia without atypia found with endometrial sampling was considered to be a benign result. At trial commencement we considered complex hyperplasia without atypia as a benign result. However, we included one woman with complex hyperplasia without atypia (inclusion number 17) in whom hysteroscopy showed an endometrial cancer. After this event, we decided to exclude women with complex hyperplasia. Other exclusion criteria were cervical cytology showing an abnormality which warranted treatment, endometrial biopsy showing a (pre) cancer or insufficient sample or if endometrial sampling had failed due to technical problems. Women using an aromatase-inhibitor or anti-oestrogen were also excluded.

Hypothesis

Uterine cavity evaluation and subsequent resection of endometrial polyps in women with postmenopausal bleeding and endometrial thickness of more than 4 mm will lead to less recurrent bleeding compared to women in whom such is not performed.

Informed consent, randomisation and masking

The local doctor or research nurse enrolled the participants and assigned them to the randomised intervention. Before randomisation participating women provided written informed consent, in which they were informed about the possible risks and complications of SIS and hysteroscopy. Women were randomised to receive either SIS and hysteroscopy or expectant management, using a web based program, using block randomisation with a block size of four, an allocation ratio of 1:1 and stratification for hospital. The web-based program generated a unique number with allocation code after entry of the patient's initials and date of birth. Neither recruiting doctors nor members of the trial project group could access the randomisation sequence. Due to the nature of the intervention the study was open-label, as it meant that masking women and doctors to the assigned intervention was not possible. The statistician doing the analysis (HZ) was masked to the assigned intervention, while those who collected follow-up data were not.

Intervention

Women allocated to diagnostic work-up all underwent SIS and hysteroscopy in the same outpatient session, within six weeks after randomisation. At SIS, a small volume of saline was inserted into the uterus, which allowed the lining of the endometrium and possible polyps to be clearly seen on an ultrasound scan. Regardless of the result, a hysteroscopy was done, using a vaginoscopic approach with a 4 to 5.5 mm hysteroscope, according to the local protocol. The hysteroscopy was performed by the local gynaecologist with experience in hysteroscopy. When a polyp was detected, immediate polypectomy was performed, by using scissors, a polyp snare or a bipolar electrode (Versapoint®). In a case of thickened or irregular endometrium, a biopsy was taken by a grasping forceps and in case of atrophic endometrium, the doctor could decide on endometrial biopsy, as this is according to the Dutch guideline[8]. When outpatient hysteroscopy was not feasible or a polyp could not be removed completely, the patient underwent hysteroscopy under regional or general anaesthesia.

Woman allocated to expectant management did not receive any specific further diagnostic work-up or treatment.

Follow-up

All women received instructions to contact the clinic in case of recurrent PMB. If a woman contacted the clinic because of recurrent bleeding, she was advised to come to the clinic. At the clinic, hysteroscopy was performed and, if present, a polyp was removed. All women were contacted by telephone after at least one year. If they had experienced recurrent bleeding, which had not been evaluated yet; they were advised to make an appointment for a hysteroscopy.

In 2014, researchers checked all case record forms. If recurrent bleeding was mentioned, but the patient had not been evaluated, the research nurse contacted the woman again and asked her to make an appointment at the clinic. To verify that women with recurrent bleeding were not missed in our registration, the researchers checked pathology-results of all included women during the study period.

Outcomes

Primary outcome measure was the recurrence of PMB within a year after randomisation. Not only real red-coloured blood loss, but also brown vaginal discharge was considered recurrent bleeding. Secondary outcome measures were time to recurrent bleeding, recurrent bleeding after more than one year and diagnostic accuracy of SIS. Although not described in the protocol as a secondary outcome the presence of polyps and the results of pathology were also registered. Precancer was defined as (simple or complex) hyperplasia with atypia.

Primary objective of this trial was to study the effectiveness of hysteroscopy in women with PMB and a thickened, benign endometrium. Because in the Netherlands, SIS can be performed together with the initial measurement of endometrial thickness and therefore is probably cheaper compared to outpatient hysteroscopy during a follow-up consultation, we studied the diagnostic accuracy of SIS as well. To do so, we performed a SIS together with the hysteroscopy if a patient was randomised in the hysteroscopy-group.

Sample size

The incidence of recurrent bleeding without hysteroscopy was assumed to be 40% based on literature.[14,16,17] Our null hypothesis assumed that the performance of hysteroscopy and polypectomy would reduce the chance of recurrent bleeding from 40% to 20%. To show such a difference, we needed to enrol 164 women (two groups of 82) (power 80%, significance level 5%). Anticipating a crossover and dropout rate of 20%, we planned to include 200 women.

Statistical analyses

Statistical analysis was performed according to the intention-to-treat principle. Differences in dichotomous outcomes were analysed with the chi-square test, or Fisher's exact test when the expected frequencies fell below five. Continuous variables were tested for normal distribution, and since none of the variables were normally distributed, a Mann-Whitney U-test for univariate analysis was used. The primary and secondary outcomes were compared by calculating relative risks (RRs) and their 95% confidence intervals (CIs). Women who were lost to follow-up were excluded in the analysis. Kaplan-Meier curves were conducted to present the time to recurrent bleeding in both groups and log-rank test was used to test differences in time to recurrent bleeding. Sensitivity and specificity for SIS were calculated, with visual hysteroscopy results (polyp yes/no) as reference standard. Women with inconclusive SIS were considered as suspicious for having endometrial pathology and have an indication for a hysteroscopy. Therefore, all women with inconclusive SIS were considered as positive result and counted as such in the sensitivity calculation.[18] For analysis, the Statistical Package for the Social Sciences (IBM Corp, Armonk, NY, USA) version 20.0 was utilised. Statistical significance was set at $p < 0.05$.

Results

During the study period 201 women presenting with postmenopausal bleeding, an endometrial thickness of > four millimetres and a benign histology result in the 12 participating hospitals, agreed to participate in the study. One woman was excluded because of use of Tamoxifen, 98 were randomly allocated to SIS and hysteroscopy and 102 women to expectant management.

The baseline characteristics of the participants in the two groups were comparable (Table 1). Of the 98 women in the SIS/hysteroscopy group, 87 underwent hysteroscopy (89%) and 11 women declined further invasive diagnostics and opted for expectant management (Figure 1). In six of these 87 women SIS was not performed, because of protocol violation. In the 102 women allocated to expectant management, all women followed the study protocol. Two of these women were lost to follow-up; we could not contact them after one year and they were excluded from analysis.

Table 1. Baseline characteristics

	Diagnostic work-up (SIS and hysteroscopy) (n = 98)	Expectant management (n = 102)
Age, years; median (IQR)	57 (54-62)	56 (52-61)
Age at menopause, years; median (IQR)	51 (48-53)	50 (48-52)
Years since menopause; median (IQR)	5 (2-12)	5 (2-11)
BMI, kg/m^2; median (IQR)	28.0 (24.3-32.7)	28.7 (25.2-35.0)
Endometrial thickness, mm; median (IQR)	8 (6-12)	7 (6-10)
Endometrial thickness measurable (%)	93 (95)	100 (98)
Episodes of bleeding		
Single (%)	66 (67.3)	77 (75.5)
Multiple (%)	32 (32.7)	25 (24.5)
Multipara (%)	87 (88.8)	93 (91.2)
Hormonal therapy		
At this moment (%)	5 (5.1)	1 (1.0)
In the past (%)	10 (10.2)	8 (7.8)
Anticoagulants	8 (8.1)	10 (9.8)
Aspirin (%)	6 (6.1)	6 (5.9)
Diabetes	7 (7.1)	7 (6.9)
with oral medication (%)	4 (57.1)	4 (57.1)
with insulin (%)	3 (42.9)	2 (28.6)
No medication (%)	0 (0.0)	1 (14.3)
Hypertension	31 (31.6)	34 (33.3)
With medication (%)	30 (96.8)	32 (94.1)
Without medication (%)	1 (3.2)	2 (5.9)
Result endometrial sampling		
Benign (%)	78 (79.6)	86 (84.3)
Polyp (%)	14 (14.3)	9 (8.8)
Simple hyperplasia (%)	5 (5.1)	7 (6.9)
Complex hyperplasia (without atypia) (%)	1 (1.0)	0
Abnormal Pap-smear (%)	4 (4.4)	3 (3.0)

IQR: Interquartile range

Figure 1 and table 2 show the findings of SIS (n=81) and hysteroscopy (n=87). In two women SIS was not possible due to pain. SIS showed a polyp in 40 women, no polyp in 33 women and was inconclusive in six women. Among these 6 women, hysteroscopy showed a benign polyp in five and one of these showed atypical hyperplasia at pathology. In the other 73 women, hysteroscopy failed in one, while a polyp was found in 41 of the 72 (57%). The sensitivity of SIS to diagnose an endometrial polyp was 93% (95% CI 0.81-0.98) for a specificity of 94% (95% CI 0.78-0.99).[18]

Figure 1. Trial flowchart

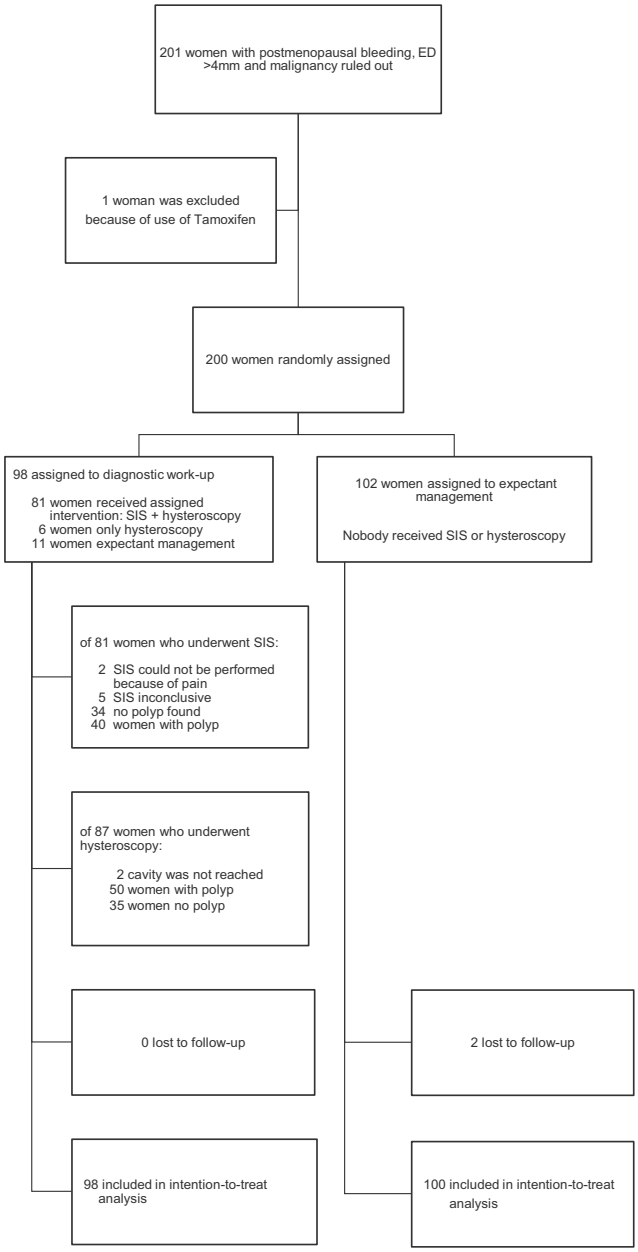


Table 2. Diagnostic accuracy of SIS as compared to the reference standard hysteroscopy
Sensitivity for SIS to diagnose an endometrial polyp 93% for a 94% specificity

		Hysteroscopy			
		Polyp	**No polyp**	**No result**	**Total**
SIS	Polyp	38	1	1	40
	No polyp	3	30	-	33
	Inconclusive	5	1	-	6
Total		46	32	1	79

In two of 87 women who underwent hysteroscopy, the cavity could not be reached by hysteroscopy because of pain and they refused hysteroscopy under general anaesthesia. In these two women a polyp could be seen in the cervical canal. Biopsy showed benign result in both cases.

Out of 85 women who underwent hysteroscopy successfully, 50 were diagnosed with a polyp (Table 3). In two women, the polyp was not sent for pathology. The pathology results of the other 48 polyps showed hyperplasia with atypia in five women and endometrial cancer in one woman, all six presenting as a focal lesion inside the polyp. Five of six women in whom the Pipelle® had missed a (pre) cancer, had SIS and in four women the polyp had been visualised, while in one woman the SIS had been inconclusive due to bad visibility. All six women with (pre) cancers were treated with hysterectomy and bilateral salpingo-oophorectomy (BSO). The final pathology result in two of the women with hyperplasia with atypia showed an endometrial cancer adding up to three women having endometrial cancer and three women having hyperplasia with atypia. All three women diagnosed with carcinoma had FIGO stage I endometroid adenocarcinoma and did not need adjuvant treatment.

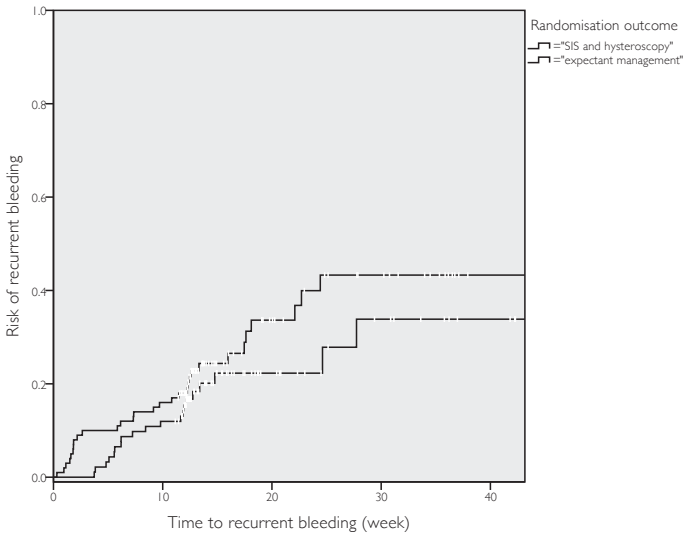
Table 3. Pathology results after hysteroscopy (and hysterectomy) in diagnostic work-up-group (n=87)

	Polyp (n=50)		**No polyp (n=35)**	**Hysteroscopy not possible (n=2)**
	Polypectomy n=45	**Biopsy n=5**	**Biopsy n=6**	**Biopsy n=2**
No result	2 (2.3)	-	-	-
Benign	35 (39.1)	5 (5.8)	6 (6.9)	2 (2.3)
Hyperplasia without atypia	2 (2.3)	-	-	-
Hyperplasia with atypia	3 (3.5)	-	-	-
Endometrial cancer	3 (3.5)	-	-	-

Numbers (percentages) of total hysteroscopies

Women with a missed diagnosis of a (pre) cancer after endometrial sampling had a significantly thicker endometrium (12 versus 8 mm (p=0.02) and a higher BMI (35.9 versus 27.5 (p=0.008)) compared to women with a true negative result of endometrial sampling. The patient characteristics of these women are detailed in the Appendix and Table A1.

Figure 2: Kaplan-Meier curves for time to recurrent bleeding in women after diagnostic work-up or expectant management.



Recurrent bleeding within 12 months occurred in 15 women (15.3%) after hysteroscopy and in 18 women (18.0%) after expectant management (RR 0.85; 95% CI 0.4-1.6) (Table 4). Follow-up varied between 12 and 56 months, with a median follow-up of 14 months in both groups. Figure 2 shows the Kaplan-Meier curve for time to recurrent bleeding. The mean time to recurrent bleeding after hysteroscopy was 34.5 weeks (95% CI 30-39) versus 30.1 weeks (95% CI 26-34) after expectant management (log-rank test p=0.20). Table 4 shows no statistical differences in the number of polyps and carcinomas found at recurrent bleeding between the women in the hysteroscopy group or the women in the expectant management group.

Table 4. Primary and secondary outcomes

	Diagnostic work-up N=98	Expectant management N=100	Relative risk	(95% CI)
Findings at randomisation				
Polyps found with hysteroscopy	50 (51.0)	0	-	-
Hyperplasia and atypia	3 (3.1)	0	-	-
Endometrial cancer	3 (3.1)	0	-	-
Findings during follow-up < 1 year				
Recurrent bleeding	15 (15.3)	18 (18.0)	0.85	(0.46-1.59)
Polyps found with recurrent bleeding	5 (5.1)	12 (12)	0.43	(0.16-1.19)
Endometrial cancer in recurrent bleeding	1	0	-	-
Findings during total follow-up				
Total recurrent bleeding	20 (20.4)	31 (31)	0.66	(0.40-1.07)
Polyps found with recurrent bleeding	8 (8.3)	15 (15)	0.54	(0.24-1.23)
Endometrial cancer in recurrent bleeding	2 (2)	1(1)	3.10	(0.30-31.98)

Data are n(%), unless otherwise indicated.

In twenty-five out of 51 women (49%) with recurrent bleeding the study protocol was followed and they underwent immediate hysteroscopy. The other 17 women were contacted again after the study was finished and were offered to undergo a hysteroscopy. Finally, four women did not receive further diagnostic work-up: three women refused hysteroscopy and one woman had died due to heart failure two years after randomisation. Further details on the women with recurrent bleeding are provided in Table A2 and Table A3. During follow-up two women in the hysteroscopy group and one woman in the expectant management group were diagnosed with endometrial cancer. Details can be found in the Appendix.

Discussion

Main findings

The results from this multicentre, open label, randomised controlled trial suggest that in women with PMB, a thickened endometrium and a benign result of endometrial sampling, there is no strict indication for hysteroscopy and/or polypectomy to reduce the risk of recurrent bleeding within one year after randomisation. The rate of (pre) cancer in women presenting with recurrent bleeding was comparable in both groups. However, we found a (pre) cancer rate of 6% in women undergoing

hysteroscopy, after an initially benign result of endometrial biopsy. A strategy using direct hysteroscopy would detect focal endometrial cancers that were initially missed. A strategy, using SIS to select women for hysteroscopy, could be effective as SIS showed a sensitivity of 93% to detect focal pathology.

Strengths and limitations

Important strengths of this study are that loss to follow-up was limited both by contacting all women after one year and by requesting pathology results of all included women. Doing this we reduced the percentage of women without any diagnostic work-up from 33% to 8%.

An important weakness is that not in all women with recurrent bleeding the study protocol (and national guideline) had been followed.[8] We found that women and also doctors were sometimes reluctant to perform hysteroscopy and that some general practitioners did not refer women with recurrent bleeding, although this is a recommendation in the national guideline. Furthermore, a potential limitation of our study is its power. When we started this study we assumed a percentage of recurrent bleeding of 40%, to be reduced to 20% after hysteroscopy, which was based on only three available studies.[14,16,17] However, the percentage of recurrent bleeding in the untreated group in this study was only 18%.

Another limitation is that we were not able to perform a thorough evaluation of the women in the expectant management group. It is to be expected, due to the nature of randomisation, that also in the expectant management group a number of women would be diagnosed with endometrial (pre) cancer. However, because this study was not funded, we were not able to call back these women for further evaluation.

Interpretation

To our knowledge this is the first randomised clinical trial that studies the effectiveness of hysteroscopy and polypectomy in women with postmenopausal bleeding. In literature there is a lack of studies on the removal of endometrial polyps, highlighting the need for randomised trials on this subject.[20]

Our initial question was whether hysteroscopy and polypectomy would reduce the probability of recurrent bleeding. A previous trial, in which we aimed to randomise women for polypectomy or not after a polyp was detected by hysteroscopy, failed as after 26 months only four women were randomised. Apparently, women as well as their doctors did not want to be exposed to no intervention once a polyp was diagnosed.[21] The present study design was based on the failed previous study.

An unexpected finding of our study is the relatively high rate of (pre) cancer after a benign endometrial sampling. Two previous meta-analyses showed the sensitivity of Pipelle® to be 97% and 99.6%, respectively.[22,23] Although both meta-analyses included pre- and postmenopausal women, the number of women with postmenopausal bleeding was limited (Clark described 314 postmenopausal women, of whom 14 had endometrial cancer. Dijkhuizen described 319 postmenopausal women, of whom 52 had endometrial cancer). All included studies used dilatation and curettage (D&C) as the reference standard,[24-28] and therefore are expected to miss 50-85% of all focal intracavitary pathology.[29,30] At present, hysteroscopy with guided biopsies is the gold standard to diagnose endometrial abnormalities.[11]

Of major importance is the clinical relevance of the diagnosis of endometrial cancer. Mingels et al recently performed histological assessment of the whole endometrium in a cohort of 48 postmenopausal women without bleeding who had hysterectomy because of a prolapse.[34] Four (8.3%) of 48 women had atypical hyperplasia while two women (3%) had a small focal endometrial cancer and in 27% an endometrial polyp was found. This suggests a higher prevalence of endometrial pathology in (asymptomatic) postmenopausal women then assumed.[35] This underscores that the relation between intracavitary pathology and postmenopausal bleeding is debatable. Although the women in our study diagnosed with atypical hyperplasia or carcinoma had hysterectomy with BSO, the clinical course of these cancers, when left untreated, is unclear. The fact that overall in this study eight women in the hysteroscopy group and one woman in the expectant group were diagnosed with a (pre) cancer, suggests that due to randomisation, we missed a few (pre) cancers in the expectant management group. This strengthens the indication for further diagnostic work-up in women with a benign result of endometrial sampling to exclude focal (pre) cancers, because endometrial sampling can miss these.

Conclusion

In women with PMB, a thickened endometrium and benign endometrial sampling, operative hysteroscopy does not reduce recurrent bleeding. However, the finding of a 6 % prevalence of (pre) cancer in an endometrial polyp, not diagnosed by endometrial sampling, indicates intracavitary diagnostics as standard procedure in these women. In alignment with other studies,[31,32] we found SIS to be accurate in the diagnosis endometrial polyps, indicating that a strategy starting with SIS triaging for hysteroscopy or not would be reasonable. Whether the initial diagnostic work-up should start with SIS, followed by endometrial sampling, or vice versa, needs

further evaluation. These findings indicate that in women with PMB, a thickened endometrium and a benign endometrial sampling, further diagnostic work-up is warranted to detect focal (pre) cancers, missed by endometrial sampling.

Appendix

Women with endometrial carcinoma during follow-up

In the first year after randomization, one woman who presented with recurrent bleeding, randomized to the hysteroscopy group, was diagnosed with endometrial cancer. This woman presented with recurrent bleeding after seven months and biopsy taken at hysteroscopy showed an endometrial carcinoma grade 1. More than 12 months after randomization, another woman in the hysteroscopy group and one woman in the expectant management group, both presenting with recurrent bleeding, were diagnosed with endometrial cancer.

Table A1. Patient characteristics of women with a missed diagnosis of atypical hyperplasia or endometrial cancer with Pipelle®

	Missed (pre) cancer (n=6)	True benign result of Pipelle® (n= 81)
Age, years; median (IQR)	63 (56-76)	57 (54-62)
BMI, kg/m^2; median (IQR)	35.9 (30.4-41.3)*	27.5 (24.3-32.2)
Years since menopause; median (IQR)	10 (4-27)	4 (2-12)
Endometrial thickness, mm; median (IQR)	12 (12-18)*	8 (6-12)

*indicates a significantly different result compared to women with a true benign result of endometrial biopsy.

The woman in the hysteroscopy group returned with recurrent bleeding two months after initial hysteroscopic removal of a benign polyp and the gynecologist advised to switch hormonal treatment, without any further diagnostic work-up. Almost two years later, this woman returned with a new episode of bleeding; diagnostic work-up by TVS and endometrial sampling showed a thickened endometrium and pathology from a biopsy taken at hysteroscopy showed atypical hyperplasia. She underwent a hysterectomy and final pathology revealed an endometrial carcinoma grade 1.

The woman with endometrial carcinoma found in the expectant management group came back with recurrent bleeding 23 months after randomization. TVS showed irregular intracavitary abnormalities and pathology (endometrial sampling) showed a grade 1 endometrial carcinoma. FIGO stage 1A endometrial carcinoma was diagnosed in all three women after hysterectomy.

Table A2. Diagnostic work-up in women with recurrent bleeding, during total follow-up

	Hysteroscopy (N=20)	Expectant management (N=31)
Diagnostic work-up at first contact with recurrent bleeding		
TVS	2 (10)	3 (9.7)
TVS+sampling	1 (5)	3 (9.7)
Hysteroscopy (+/- histology)	6 (30)	19 (61.3)
No work-up	11 (55)	6 (19.4)
Reason for no diagnostic work-up		
Patient	5 (25)	4 (12.9)
General practitioner	3 (15)	2 (6.5)
Gynaecologist	3 (15)	
Diagnostic work-up total follow-up		
TVS	4 (20)	3 (9.7)
TVS + sampling	3 (15)	4 (12.9)
Hysteroscopy (+/- histology)	11 (55)	22 (71)
No work-up	2 (10)	2 (6.5)
Reason for no hysteroscopy		
Patient	5 (25)	1 (3.2)
Endometrium <4 mm	4 (20)	5 (16.1)
Benign result endometrial sampling	1 (5)	1 (3.2)
Carcinoma in endometrial sampling	1 (5)	-
Definite pathology result		
Benign	4 (20)	5 (16.1)
Benign polyp	7 (35)	15 (48.4)
Endometrial cancer	2 (10)	1 (3.2)
No result	7 (35)	10 (32.3)

Numbers (percentages of women with recurrent bleeding)

Table A3. Patient characteristics of women with recurrent bleeding within the first year after randomisation

	Recurrent bleeding <1 year n=51	No recurrent bleeding < 1 year=147
Median age (IQR), years	56 (53-63)	57 (54-61)
Median (IQR) BMI, kg/m^2	28.5 (25.1-34)	28.7 (24.3-33.7)
Median (IQR) years since menopause	4 (2-13)	5 (2-11)
Median (IQR) endometrial thickness, mm	6 (5-9)*	8 (6-12)

*indicates significantly different result by comparing with women without recurrent bleeding in the first year.

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Chapter 6

Cost-effectiveness of the diagnostic work-up for postmenopausal bleeding: a randomised controlled trial

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Manuscript in preparation

Abstract

Objective To evaluate the cost-effectiveness of hysteroscopic treatment of endometrial polyps versus expectant management in women with postmenopausal bleeding and a thickened endometrium with a benign result of endometrial sampling.

Materials and methods An economic evaluation was performed alongside a randomised trial. Women with postmenopausal bleeding and an endometrial thickness > 4 millimetres with a benign result of endometrial sampling, had been randomised into a group receiving further diagnostic work-up by hysteroscopy (combined with preceded saline infusion sonography) and a group receiving expectant management. Primary clinical outcome was recurrent bleeding within 12 months. In the hysteroscopy group, the presence of polyps and the results of their histology were registered. Outcomes for the cost-effectiveness analysis were cost-differences and incremental cost-effectiveness ratios for both the prevention of recurrent bleeding and detecting of endometrial (pre) cancers. Statistical uncertainty in the cost-effectiveness analyses was estimated using bootstrapping.

Results Costs were statistically significantly higher in the hysteroscopy-group compared to the expectant management group (€ 888 versus € 108, cost difference € 780 (95% 550; 1158)). There was no statistically significant difference in the number of women with recurrent bleeding (15 % versus 18 %, -3%, 95% CI -13; 8%). The CEA for the detection of endometrial (pre) cancers during a follow-up of 12 months showed a statistically significant effect difference (7% (95% CI 3; 14%)). In the hysteroscopy group, the ICER to detect one case of (pre) cancer was € 10,917. Decision makers should be willing to pay €19,500 to detect one cancer extra to reach a probability of cost-effectiveness of 0.95.

Conclusion In women with postmenopausal bleeding, a thickened endometrium and benign endometrial sampling, operative hysteroscopy does not reduce recurrent bleeding but detects focal endometrial (pre) cancer in 7% of these women. The capacity of hysteroscopy in all patients to identify (pre) cancers comes at a price of around € 11,000 euro per woman identified with (pre) cancer.

Trial registration Dutch trial register number NTR2130.

Introduction

Postmenopausal bleeding (PMB) is a common symptom encountered in gynaecological practice[1]. Because about 10% of these women have an underlying endometrial cancer,[2,3] the diagnostic work-up focuses on diagnosing or ruling out endometrial cancer. To distinguish between women with a low- or high risk for endometrial cancer, measurement of endometrial thickness is used with a high accuracy.[4-6] If the endometrium is thickened the woman is considered to have a high risk, and endometrial sampling is performed to obtain a histological diagnosis.[7]

Current guidelines leave room for individual doctors and patients to decide on the next step when endometrial sampling shows a benign result.[8-10] Saline infusion sonography (SIS) and hysteroscopy are used for the detection and removal of benign endometrial polyps, which are a potential cause of recurrent bleeding.[11,12] Hysteroscopy, despite being safe, well tolerated and performed in an outpatient setting, remains an invasive procedure with a potential risk of complications and at considerable cost[11]. Therefore, some doctors and patients prefer expectant management over immediate hysteroscopy.

We performed a randomised clinical trial in which we randomised women with PMB to expectant management or further diagnostic work-up by SIS and hysteroscopy. This trial showed no difference in the number of women presenting with recurrent bleeding, within the first 12 months after randomization. However, we found that 6% of women undergoing hysteroscopy were diagnosed with a (pre) cancer of the endometrium, leading to a false negative rate of 6% of endometrial sampling. This is higher than anticipated based on current literature.[13-15] The conclusion of our trial is that in women with PMB, a thickened endometrium and a benign result of endometrial sampling, further diagnostic work-up seems to be warranted to detect focal endometrial (pre) cancers that are missed by endometrial sampling.[16]

However, it is unclear which diagnostic strategy is most efficient with regard to costs and effects. Therefore, the aim of this paper was to evaluate the cost-effectiveness of the diagnostic work-up by hysteroscopy (preceded by SIS) compared to expectant management over a 12-month period in women with PMB, a thickened endometrium and a benign result of endometrial sampling in order to prevent recurrent postmenstrual bleeding and detected (pre) cancers.

Methods

The economic evaluation was conducted alongside a randomised clinical trial with 12 months of follow-up that was performed between January 2010 and October 2013. The trial was performed within the Dutch Consortium for research in Women's Health, a collaboration of teaching and non-teaching hospitals in the Netherlands.[17] Full details about the trial protocol can be found at www.studies-obsgyn.nl/pompoen.

The trial was registered at the Dutch trial register (NTR2130). Approval for this study was obtained from the Medical Ethical Committee of the Academic Medical Centre, Amsterdam (MEC 2008-177) and from the Central Committee on Research involving Human Subjects (CCMO), The Netherlands. The local board of each participating hospital approved the study. The methodological details of the trial are reported in detail in a previous paper and are only briefly summarised here.[16]

Participants

Women could be included if they had PMB, an endometrial thickness of > 4 mm and benign histology. Simple hyperplasia without atypia in the endometrial sample was defined as benign histology.

Randomisation

Consenting women were randomly assigned to receive either further diagnostic work-up by SIS and hysteroscopy or expectant management, using a web-based randomisation program, stratification for hospital.

Interventions

Women allocated to diagnostic work-up all underwent SIS and hysteroscopy in the same office session. Regardless of the result of the SIS, a hysteroscopy was done. When a polyp was detected, immediate polypectomy was performed. In case of an atrophic endometrium, the doctor could decide on endometrial biopsy. When office hysteroscopy was not feasible or a polyp could not be removed, the patient underwent hysteroscopy under regional or general anaesthesia.

Women allocated to expectant management did not receive any specific further diagnostic work-up or treatment. All women received instructions to contact the clinic in case of recurrent postmenopausal bleeding. At the clinic, further diagnostic work-up by hysteroscopy was performed and, if present, a polyp was removed.

Clinical outcomes

The primary outcome measure was the recurrence of PMB within a year after randomization. All women were contacted by telephone after one year to assess whether they had experienced recurrent bleeding. Although not registered as a secondary outcome in the protocol, pathology results of hysteroscopy showing the presence of a (pre) cancer were also registered. Since no hysteroscopy was performed in the group receiving expectant management, we assumed that the prevalence of (pre) cancer in this group was the same as in the group receiving a diagnostic work-up with hysteroscopy and a SIS due to the randomization principles.

Costs

Costs were assessed from a healthcare perspective and were derived from case record forms. Direct health care costs directly after inclusion (diagnostic work-up) in the study included visits to the outpatient clinic, costs for diagnostic or therapeutic hysteroscopy and costs for diagnosis and treatment of a (pre) cancer of the endometrium diagnosed with hysteroscopy after randomisation. Direct health care costs during follow-up included visits to the outpatient clinic, transvaginal sonography (TVS), diagnostic or therapeutic hysteroscopy and costs for diagnosis and treatment of a (pre) cancer of the endometrium diagnosed during 12 months follow-up. Prices were based on Dutch standard costs if available.[18] In other cases, prices were obtained from the financial administration of one of the participating academic hospitals. All costs were adjusted to the year 2012 using consumer price indices if necessary.[19] Discounting was not necessary, because follow-up was limited to 12 months. Table 1 lists the cost categories and prices used in this economic evaluation.

Diagnostic work-up strategies

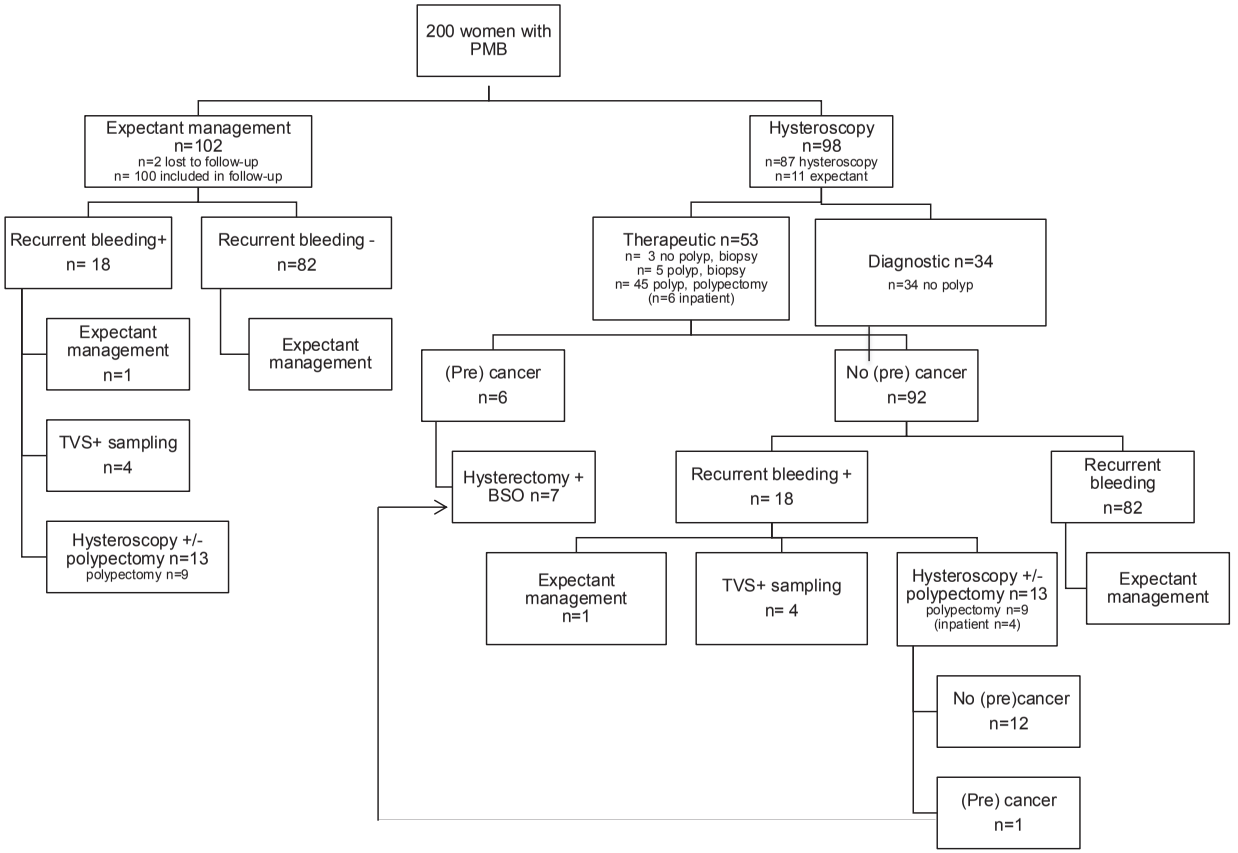
In this paper, we compared two strategies with expectant management: a strategy in which all women received a hysteroscopy without a SIS and a hypothetical strategy in which all women received a SIS and only those with a suspicion of an endometrial polyp or an inconclusive SIS underwent a hysteroscopy.

Table 1. Cost categories and prices (€) used in this economic evaluation (2012)

Category	Price (€)	Total price (€)	Source
Outpatient visit	76.44	76.44	NHI
Ultrasound	39.40	39.40	DHA
Outpatient Pipelle		67.57	
Pipelle	4.79		MUMC
Pathology	62.78		NHI
Outpatient SIS		47.24	
Ultrasound	39.40		DHA
SIS catheter + NaCl/gel	7.84		MUMC
Outpatient diagnostic hysteroscopy		267.82	
30 minutes outpatient clinic	150.00		NHI
Personnel			NHI
Gynaecologist (30 min)	69.86		
Outpatient nurse (30 min)	15.02		
Resident gynaecology (30 min)	14.89		
Sterilisation hysteroscopy-set	18.06		MUMC
Outpatient hysteroscopy + biopsy		330.60	
Diagnostic hysteroscopy	267.82		
Pathology	62.78		DHA
Outpatient hysteroscopy + polypectomy		610.37 / 394.27	
Diagnostic hysteroscopy +pathology	330.60		
Versapoint / polyp snare	279.77 / 63.67		MUMC
Inpatient hysteroscopy + polypectomy		1322.51	
Day-admission	266.48		NHI
45 minutes OR + overhead (42%)	450.00 +189.00		NHI
Personnel OR 45 min			NHI
Gynaecologist+ Anaesthetist	209.58		
Anaesthetic + OR nurses (3x)	104.28		
Resident gynaecology	22.33		
Sterilisation hysteroscopy-set	18.06		MUMC
Pathology	62.78		DHA
Chest X-ray		50.77	DHA
Vaginal hysterectomy		3648.27	
Hospital admission, 2 days	970.37		NHI
90 minutes OR +overhead	1704.00		NHI
Personnel OR 90 minutes	893.06		NHI
Sterilisation hysterectomy-set	18.06		MUMC
Pathology	62.78		DHA
Laparoscopic hysterectomy + BSO,		4845.83	
Hospital admission, 2 days	970.37		NHI
120 minutes OR +overhead	2130.00		NHI
Personnel OR 120 minutes	1116.33		NHI
Sterilisation hysterectomy-set	18.06		MUMC
Disposables	548.29		MUMC
Pathology	62.78		DHA

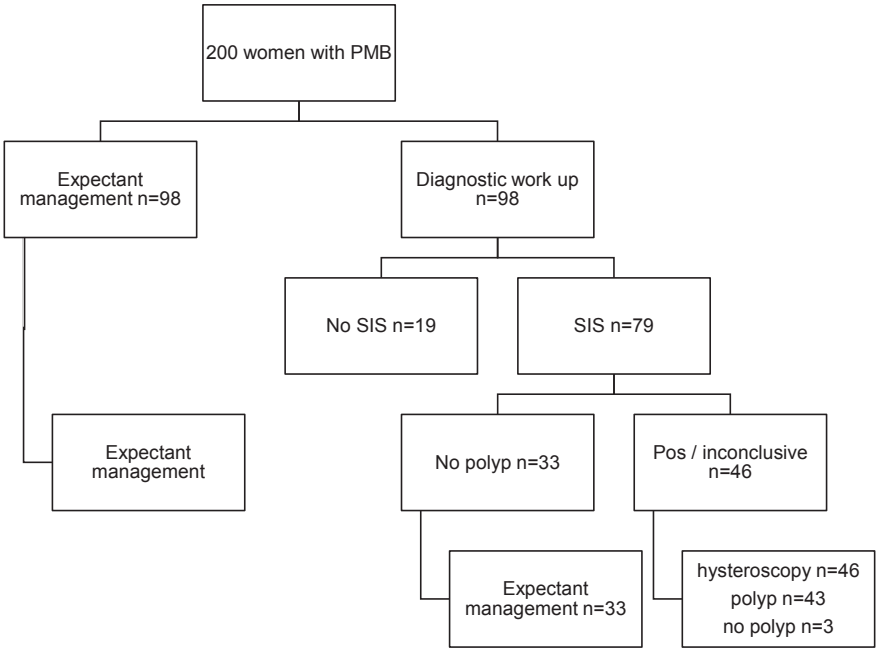
DHA = Dutch Healthcare Authority, MUMC = Maastricht University Medical Centre, NHI = National Healthcare Institute

Figure 1. Study flowchart



It was assumed that effects in this strategy would be the same as in the hysteroscopy only strategy, as SIS was shown to have high diagnostic accuracy (sensitivity 93% and specificity 94%).[16] In this scenario, an inconclusive SIS was followed by a hysteroscopy. The different strategies are shown in Figure 1 and 2.

Figure 2. Hypothetic strategy using SIS to select women for hysteroscopy



Cost-effectiveness analysis

The cost-effectiveness analyses were performed according to the intention-to-treat principle. Imputation was not necessary, because complete data were available for all participants. Incremental cost-effectiveness ratios (ICERs) were calculated by dividing the difference in costs between the two intervention groups by the difference in effects, resulting in an estimate of the additional costs associated with one case of recurrent blood loss prevented and with one carcinoma extra detected.

Differences in costs and effects between the two intervention groups were estimated using bivariate regression models to account for the possible correlation between costs and effects. Because of the skewed distribution of costs, bias-corrected and accelerated bootstrapping was used to estimate 95% confidence intervals around cost differences and to estimate statistical uncertainty surrounding

the ICERs. The bootstrapped cost-effect pairs were plotted on a cost-effectiveness plane (CE plane) and used to estimate cost-effectiveness acceptability curves (CEA curves). On a CE plane, the bootstrapped effect differences are plotted on the x-axis and the bootstrapped cost differences are plotted on the y-axis thereby visually showing the uncertainty surrounding the ICER[20]. CEA curves show the probability that the intervention is cost-effective in comparison with the control treatment for a range of ceiling ratios. The ceiling ratio is defined as the amount of money society is willing to pay to gain one unit of effect.[21]

Results

Patients

During the study period, 200 postmenopausal women with uterine bleeding were included, of whom 98 were randomly allocated to SIS and hysteroscopy and 102 women to expectant management. There were no statistically significant or clinically relevant differences in patient characteristics between the two groups. Details on patient characteristics in this study can be found in the original publication.[16] The patient flow of this study is presented in Figure 1.

Clinical outcomes

Table 2 shows the results of the analyses of clinical outcomes. After 12 months, recurrent bleeding between the two groups was not statistically significant, with 18 (18%) women in the hysteroscopy group presenting with recurrent bleeding compared to 15 (15.3%) women in the expectant management group. The definite pathology result of six of these 50 women, in whom an endometrial polyp was found, showed a (pre) cancer: three women having FIGO stage I endometroid adenocarcinoma and three women having atypical hyperplasia. During the follow-up period of 12 months one other woman was diagnosed with a FIGO stage I endometrioid adenocarcinoma in the hysteroscopy group as well. Thus, in the hysteroscopy group 6% of women were diagnosed with an endometrial (pre) cancer at initial work-up and another one woman was diagnosed with endometrial cancer during follow-up. This makes a total of 7% (pre) cancers detected during 12 months of follow-up in the hysteroscopy group. Assuming that the prevalence of endometrial cancer was the same in the expectant management group, this constitutes a statistically significant difference in detected carcinoma between the groups (difference 7%, 95% CI 3% to 14%).

Table 2. Effects and costs after 12 months for hysteroscopy versus expectant management

Outcome	Expectant management (n=100)	Hysteroscopy (n=98)	difference (95% CI)
Recurrent bleeding during 12 months follow-up	18 (18.0)	15 (15.3)	-3% (-13 - 8%)
(Pre) cancer at randomization - hysteroscopy	0	6 (6.9)	-
(Pre) cancer during 12 months follow-up	0	1	-
Direct healthcare costs, initial work-up, mean € (SD)	0 (0)	788 (1333)	788 (585 - 1132)
Direct healthcare costs, follow-up recurrent bleeding, mean € (SD)	108 (365)	100 (567)	-8 (-106 - 185)
Total costs, mean € (SD)	108 (365)	888 (1435)	780 (550 - 1158)

Costs

Costs (in euros) in the hysteroscopy and the expectant management group are also shown in Table 2. The greatest contributors to the total costs were the costs for the treatment of the women diagnosed with a (pre) cancer. Direct healthcare costs for diagnostic work-up were significantly higher in the hysteroscopy group (€ 788 versus € 0, mean difference € 788, 95% CI € 585 to € 1132). There was no statistically significant difference in direct healthcare costs during follow-up, resulting in total health care costs over 12 months of € 888 versus € 108 (mean difference € 780, 95% CI 550 to 1158).

Table 3. Summary of results for effectiveness (recurrent bleeding, detection carcinoma), costs (of diagnosis and treatment, in euros per patient) and incremental cost-effectiveness ratio

Outcome	Scenario	ΔE (95% CI)	ΔC (95% CI)	ICER	CE plane			
					NE	SE	SW	NW
Recurrent blood loss	Without SIS	-0.03 (-0.13 ; 0.08)	780 (550 ; 1158)	28865	69%	0%	0%	31%
Detection of carcinoma	Without SIS	0.07 (0.03 ; 0.14)	780 (550 ; 1158)	10917	100%	0%	0%	0%
	With SIS*	0.07 (0.03 ; 0.14)	634 (408 ; 996)	8913	100%	0%	0%	0%

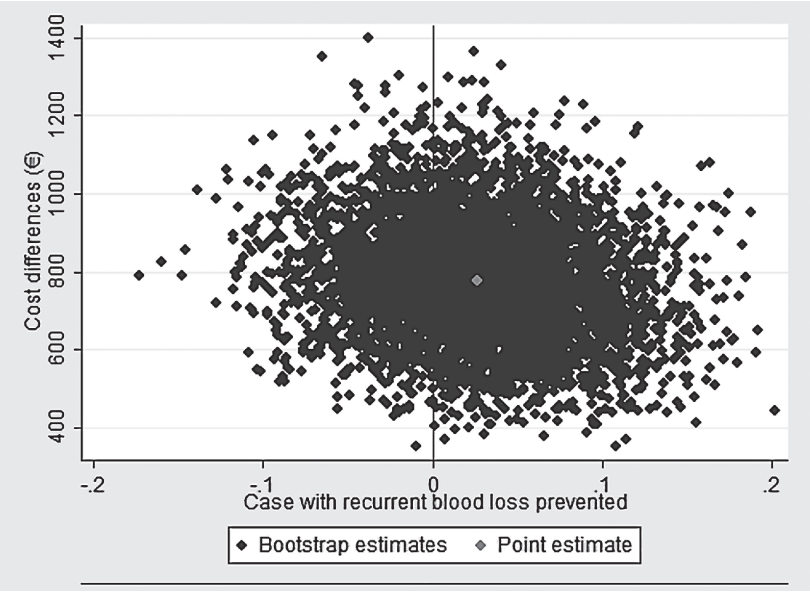
ΔE = effect ; ΔC = costs; ICER = incremental cost-effectiveness ratio in Euros

Diagnostic strategy consisting of direct hysteroscopy

The ICER for recurrent bleeding shows that to prevent one case with recurrent bleeding € 28,865 should be invested in the hysteroscopy group as compared with the expectant management group (Table 3). The CE plane in Figure 3a shows that there is considerable uncertainty around the ICER, but confirms the statistically

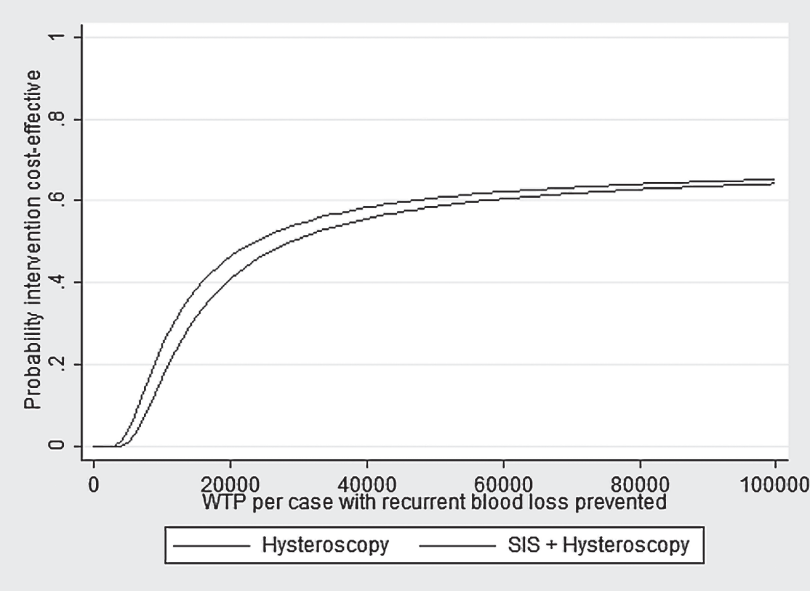
non-significant effect difference (bootstrapped cost-effect pairs distributed across the eastern and western quadrants of the plane) and the statistically significant cost difference (all bootstrapped cost-effect pairs located in the northern quadrants of the plane). The CEA curve (Figure 3b) shows that at willingness-to-pay values of € 0, 5,000 and 10,000 /case with recurrent blood loss prevented the probability that the intervention is cost-effective in comparison with usual care is 0, 0.01 and 0.17, respectively. The maximum probability that the intervention is cost-effective in comparison with expectant management is 0.69 at a willingness-to-pay of 1,200,000 € /case of recurrent bleeding prevented.

Figure 3a. Cost-effectiveness plane for number of women with recurrent PMB during 12 months (hysteroscopy vs expectant management)



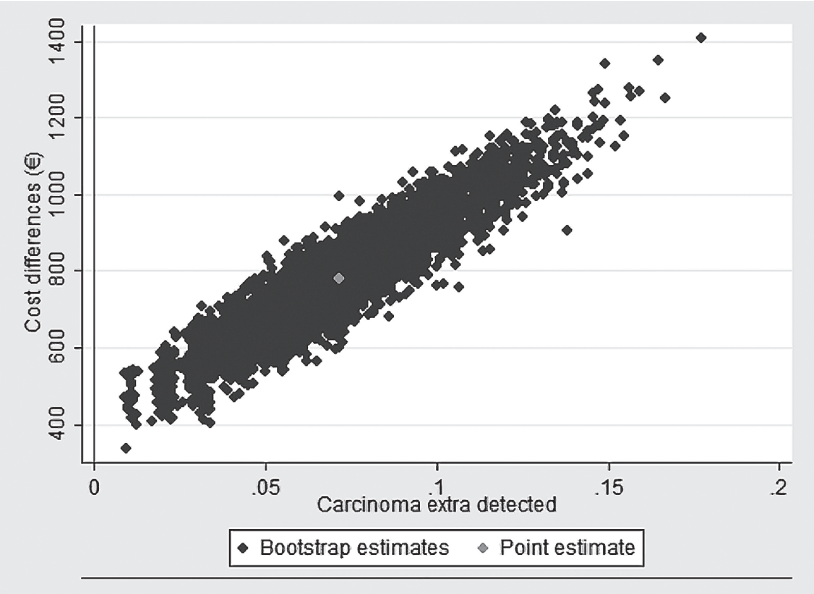
The light dot indicates the point estimate of the ICER and the dark dots indicate the bootstrapped cost-effect pairs to reflect the uncertainty around the ICER (ICER, Incremental Cost-Effectiveness Ratio).

Figure 3b. Cost-effectiveness acceptability curve for number of women with recurrent bleeding during 12 months of follow-up



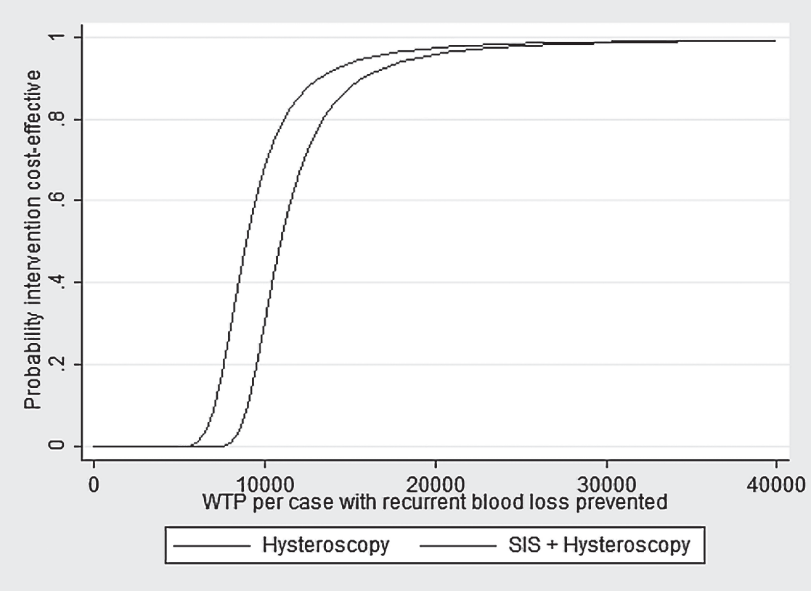
The ICER for detected carcinoma shows that to detect one case of (pre) cancer € 10,917 should be invested in the hysteroscopy group as compared with the expectant management group (Table 3). The CE plane in Figure 4a shows that there is some uncertainty around the ICER, but confirms the statistically significant effect difference (bootstrapped cost-effect pairs distributed across the eastern quadrants of the plane) and the statistically significant cost difference (all bootstrapped cost-effect pairs located in the northern quadrants of the plane). The CEA curve (Figure 4b) shows that at willingness-to-pay values of € 5,000 or 10,000 or 20,000/detected (pre) cancer extra the probability that the intervention is cost-effective in comparison with usual care is 0, 0.31 and 0.96, respectively. At a willingness to pay of 19,500 € / detected (pre) cancer extra, the probability of cost-effectiveness is 0.95.

Figure 4a. Cost-effectiveness (CE) plane for number of women with (pre) cancer during 12 months (hysteroscopy versus expectant management)



The light dot indicates the point estimate of the ICER and the dark dots indicate the bootstrapped cost-effect pairs to reflect the uncertainty around the ICER (ICER, Incremental Cost-Effectiveness Ratio).

Figure 4b. Cost-effectiveness acceptability curve for number of women with endometrial (pre) cancer diagnosed during 12 months of follow-up



Diagnostic strategy consisting of SIS and hysteroscopy

In this hypothetical strategy, we select women based on a positive or inconclusive result on the SIS to have an indication for hysteroscopy (see Figure 1). Costs per patient in the hysteroscopy group were statistically significantly higher compared to the expectant management group (mean difference € 634, 95% CI 408; 996).

The ICER for cancers detected shows that to detect one case of (pre) cancer € 8,913 should be invested in the SIS + hysteroscopy group as compared with the expectant management group (Table 3). The CEA curve (Figure 3b) shows that at willingness-to-pay values of € 5,000 or 10,000 or 20,000/case of recurrent bleeding prevented the probability that the intervention is cost-effective in comparison with usual care is 0, 0.68 and 0.97, respectively. At a willingness to pay of 16,000 € / detected (pre) cancer extra, the probability of cost-effectiveness is 0.95.

Discussion

Principal findings

In this study, we evaluated the cost-effectiveness of hysteroscopy in comparison to expectant management in women with postmenopausal bleeding, a thickened endometrium and a benign result of endometrial sampling to prevent recurrent bleeding and to diagnose an endometrial (pre) cancer. The results show that costs in the intervention group were statistically significantly higher in the hysteroscopy-group compared to the expectant management group, although the effect difference in the number of women with recurrent bleeding was not statistically significant different between the two groups.

Based on the CEA curves, hysteroscopy is not considered cost-effective to prevent recurrent bleeding. However, a direct diagnostic work-up with a hysteroscopy led to a statistically significant increase in the number of detected (pre) cancers. Detection of one case of (pre) cancer needs almost an investment of € 10,917 in the hysteroscopy group as compared with the expectant management group. The CEA curve showed the probability for hysteroscopy alone to be cost-effective in comparison with expectant management is 0.95 at a willingness-to-pay of € 19,500 /detected pre (cancer) and for hysteroscopy preceded by a SIS € 16,000 / detected (pre) cancer. We can conclude that a strategy using SIS to select women for hysteroscopy the costs to detect one case of (pre) cancer can be, depending on the probability to be cost-effective, lowered with € 2,000 to € 3000.

Strengths and weaknesses

This study is the first economic analysis that prospectively compared hysteroscopy with expectant management in women with PMB, a thickened endometrium and a benign result of endometrial sampling alongside a randomised trial. Moreover, this trial was performed in a pragmatic fashion increasing external validity of the trial.

A limitation of this economic evaluation is that important cost components are based on the prices of one university hospital in the Netherlands. We limited the economic evaluation to a hospital perspective in which only direct health care costs were taken into account. It is possible that costs of treatment of endometrial cancer or follow-up strategies differ between hospitals or countries and, therefore, our results cannot unconditionally be generalised to all circumstances. Indirect costs such as the value of lost productivity from time off work were not included in this study. However, especially in women in whom a (pre) cancer was detected these costs may be substantial. Therefore, the costs estimated in this trial are probably an underestimation of the societal costs of performing a direct hysteroscopy as compared to expectant management.

Another limitation is the power of this study. When we started the randomised trial, we assumed a percentage of recurrent bleeding of 40% that was reduced to 20% after hysteroscopy. This estimate was based on three available studies.[22-24] However, the percentage of recurrent bleeding in the untreated group in this study was only 18%.

The prevalence of 6% (pre) cancer in a preselected group of women with PMB with a benign result of endometrial sampling is higher than anticipated based on previous literature.[13-15] An explanation for this could be that in these meta-analyses only a small number of postmenopausal women were included and that blind dilatation and curettage (D&C) was used as a reference standard. D&C is nowadays almost completely replaced by hysteroscopy, because we know that D&C misses 50-85% of all focal intracavitary pathology.[25,26] Another explanation could be that the prevalence of endometrial (pre) cancers is different in different populations.[2,3,27]

In this study we assumed that the prevalence of endometrial cancer was the same in the expectant management group, based on randomisation principles. Moreover, it was assumed that effects in this strategy would be the same as in the hysteroscopy only strategy. Although our study shows that SIS has high specificity and sensitivity (94% and 93%, respectively), SIS cannot be considered to be 100% reliable. Thus, it is possible that in the SIS strategy one or more (pre) cancers would have remained undetected.

Finally, this study was not powered for the detection of endometrial cancer and this could also be a coincident finding. More research is needed on the prevalence of focal endometrial (pre) cancers in large cohorts of women.

Comparison to other studies

To our knowledge this is the first economic evaluation in which strategies using SIS or direct hysteroscopy in women with a thickened endometrium and benign result of endometrial sampling are studied. Clark et al performed a study in which they analysed cost-effectiveness of different strategies in the diagnostic work-up in women with PMB.[28] They concluded that compared to undertaking no initial investigation when a woman presents with PMB, a strategy using TVS with a 5 mm cut-off was the least expensive and that strategies using outpatient hysteroscopy were not cost-effective. However, these results are difficult to compare with this study, because Clark et al used survival as the primary outcome measure instead of recurrent bleeding or the diagnosis of endometrial (pre) cancer.[28]

In a study by Dijkhuizen et al a strategy using SIS in all women to select for therapeutic hysteroscopy was cost-effective in comparison with immediate hysteroscopy in all women. The primary outcome in this study was successful treatment (i.e. no bleeding), however, this study was performed in premenopausal women and therefore not applicable on a postmenopausal population.[29]

Breijer et al performed an economic analysis in which they studied different strategies based on patient characteristics of women with PMB. They concluded that a strategy in which patients are selected for TVS or direct endometrial biopsy based on patient characteristics is the most cost-effective strategy. Their primary outcome was five-year survival. Comparison to our results is again difficult because of a different outcome measure and because both SIS and hysteroscopy were not studied.[30]

Unanswered questions and future research

Because the number of patients with an endometrial (pre) cancer in this study is limited, the results of this study only suggest that in women with PMB, a thickened endometrium and a benign endometrial sampling further diagnostic work-up is indicated to diagnose possible focal endometrial (pre) cancers, that the costs to detect one woman with an endometrial (pre) cancer are € 10,917 and that a strategy using SIS is cheaper than a strategy using direct hysteroscopy. More research with larger cohorts of patients is needed.

Also more research is needed on the strategy using SIS. In most hospitals in the Netherlands, patients who are diagnosed with an endometrial (pre) cancer present at the outpatient clinic with PMB. During this appointment a TVS is performed and if the endometrium is > 4 mm, an endometrial sample is taken. In the same session it would be possible to perform a SIS. However, the diagnostic accuracy of the tests in case SIS and endometrial sampling are combined is still unknown. One study reported that the proportion of adequate endometrium samples that can be evaluated by the pathologist is higher when endometrial aspiration is done first with subsequent SIS, in a mixed population of pre- and postmenopausal women.[31] Thus, the optimal sequence of TVS and SIS in combination with endometrium sampling in women with postmenopausal women needs to be elucidated.

Conclusion

Our results show that hysteroscopy is not cost-effective in comparison with expectant management in the prevention of recurrent bleeding. Furthermore, our results show that with a strategy using hysteroscopy in all women with a thickened endometrium and benign endometrial sampling, incremental costs per (pre) cancer detected are around € 11,000 as compared to expectant management. A strategy using SIS to select women for therapeutic hysteroscopy, is about € 2,000 less expensive per (pre) cancer detected. CEA curves showed that the probability for hysteroscopy alone to be cost-effective in comparison with expectant management is 0.95 at a willingness-to-pay of € 19500 /detected (pre) cancer and for hysteroscopy preceded by a SIS € 16000 /detected (pre) cancer. Thus, decision makers need to decide whether they are willing to pay this amount of money to detect a (pre) cancer. Further research is required to confirm the findings of this study and to elucidate the role of SIS in the diagnostic work-up of women who present with PMB at the outpatient clinic.

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Chapter 7

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.

Introduction

Postmenopausal bleeding (PMB) is one of the most frequent complaints with which women present in the outpatient gynaecology 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 therefore no email address of the corresponding author was mentioned, we searched the internet (Google, PubMed) for an email address 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 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 sampling

without knowledge of the results of the reference test had to be clearly stated, and the histology results had to be pre-specified. For the reference standard (D&C or hysteroscopy) it had to be clearly stated that results were interpreted without knowledge of the result of endometrial sampling. For patient flow and timing, the time between endometrial sampling and reference test, if all patients received the same reference test and if all patients were included in the analysis, had to be clearly stated. Applicability was based on patients with PMB, endometrial sampling as the index test, D&C or diagnostic hysteroscopy with histology as reference test.

For all articles, each domain was assessed in terms of risk and bias, and the first three domains were also assessed in terms of applicability for this review. Each item was labelled 'low', 'high', or 'unclear'. Studies, which scored 'high bias' on more than one of four items, were excluded. And only studies, which scored 'low' on all three items of concerns on applicability, were included in this review. We included all applicable studies on this subject, regardless of the number of postmenopausal women included and regardless if data were collected prospectively or retrospectively.

Data extraction

For studies, which included pre- and postmenopausal women, we used only those calculations and conclusions concerning the latter. From each article we extracted (if available): the reference standard that was used, the number of women who underwent endometrial sampling, the number of women in whom endometrial sampling was not possible, failed or showed insufficient material for a pathologic diagnosis, the number of women who underwent both endometrial sampling and the reference standard, the number of cases with endometrial cancer, atypical hyperplasia or endometrial disease. Hyperplasia without atypia was considered a benign result. Endometrial disease was defined as benign endometrial polyps in one study, and as polyps, hyperplasia and cancer together in most other studies. For this meta-analysis we decided to define endometrial disease as endometrial cancer, atypical hyperplasia and benign endometria polyps together as endometrial disease.

Data analysis

For each study, we calculated the percentage of women in whom endometrial sampling failed to provide a diagnosis, either due to the possibility to obtain tissue (for example, because of cervical stenosis) or due to the fact that the sample that was obtained was insufficient for the pathologist to establish a diagnosis. We described the number of endometrial cancers in women with a failed endometrial sampling.

For studies that had numbers available, we constructed 2 x 2 tables and calculated sensitivity and specificity for the diagnosis of endometrial cancer, atypical hyperplasia or endometrial disease. Sensitivity and specificity were calculated for the cases in which both endometrial sampling as well as the reference test was successful. We calculated the weighted sensitivity, taking into account the size of each study, compared to the two different reference strategies. When a 2x2 table could be constructed, we plotted the sensitivity against the '1- specificity' in a receiver-operating curve (ROC).

Results

Study selection

Our systematic search identified 499 titles. After exclusion of studies, which did not exist online anymore and exclusion of duplicates, we identified 377 articles, of which 65 articles were found to be relevant (Figure 1). After reading these 65 articles in full-text, we could include 11 studies that reported on postmenopausal women only, 2 articles that described data on postmenopausal women separately in a total population of perimenopausal women and 17 articles that compared the results of endometrial sampling with histology findings from (blind) D&C or diagnostic hysteroscopy in a combined population of pre- and postmenopausal women.

In none of the 17 studies that reported on a combination of pre- and postmenopausal women, we were able to contact the corresponding author. In 10 studies these authors did not respond, while contact details were not available for the other 7 studies. Therefore, we had to exclude these 17 studies from the meta-analysis. The initial agreement of the two reviewers (NvH and MMP) regarding eligibility was 94% (weighted kappa 0.88 (95% CI 0.76-0.99)).

Figure 1. Study selection flowchart

*The reference list for excluded studies is available from the corresponding author.

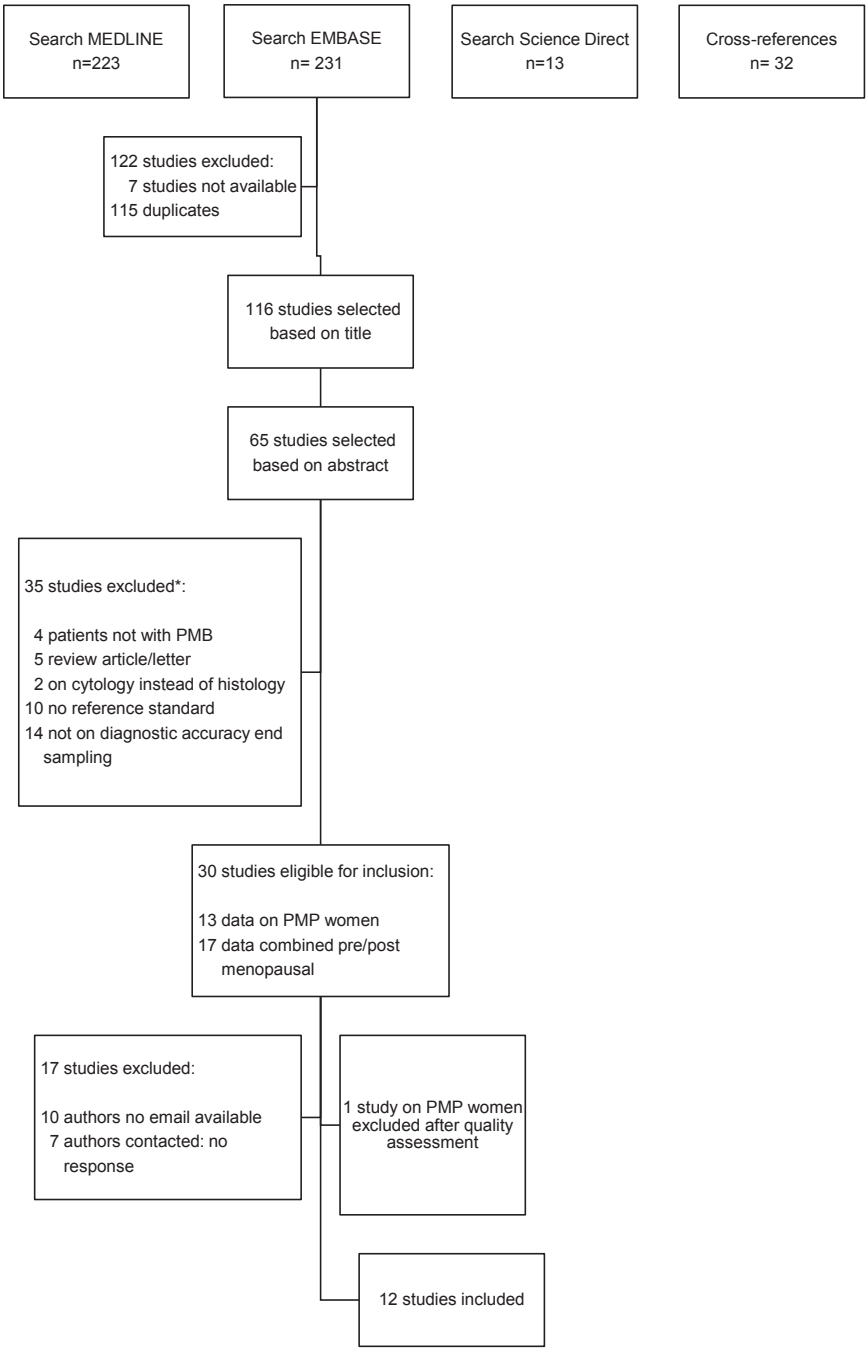


Table 1. Study characteristics of the twelve included studies on the diagnostic accuracy of endometrial sampling

	Study design	Patient selection	Index test	Reference standard	Menopausal status	PMB n	HRT %
Goldberg 1982	Prospective	Unclear	Vabra & Accurette	Blind D&C	Post	40	Nr
Batool 1994	Prospective	Unclear	Pipelle	Blind D&C	Post	70	Nr
Ben-Baruch 1994	Retrospective	Unclear	Pipelle	Blind D&C	Pre & post	90	Nr
vdBosch 1995	Prospective	Consecutive	Pipelle	Hysteroscopy w/ histology	Post	140	0
vdBosch 1996	Prospective	Consecutive	Pipelle	Hysteroscopy w/ histology	Post	87	0
Giusa-Chifieri 1996	Prospective	Unclear	Novak	Hysteroscopy w/ histology	Post	80	Nr
Gupta 1996	Prospective	Consecutive	Pipelle	Hysteroscopy w/ histology	Post	76	0
De Silva 1997	Prospective	Consecutive	Pipelle	Hysteroscopy w/ histology	Post	50	Nr
Mortakis 1997	Not reported	Unclear	Pipelle	Hysteroscopy w/ histology	Pre & post	78	0
Bunyavejchevin 2001	Prospective	Unclear	Pipelle	Blind D&C	Post	30	0
Epstein 2001	Prospective	Consecutive	Endorette	Blind D&C	Post	133	56
Spicer 2006	Prospective	Consecutive	Accurette	Hysteroscopy w/ histology	Post	136	Nr

D&C=dilatation and curettage; PMB=number of women with postmenopausal bleeding; Nr=not reported

Quality assessment

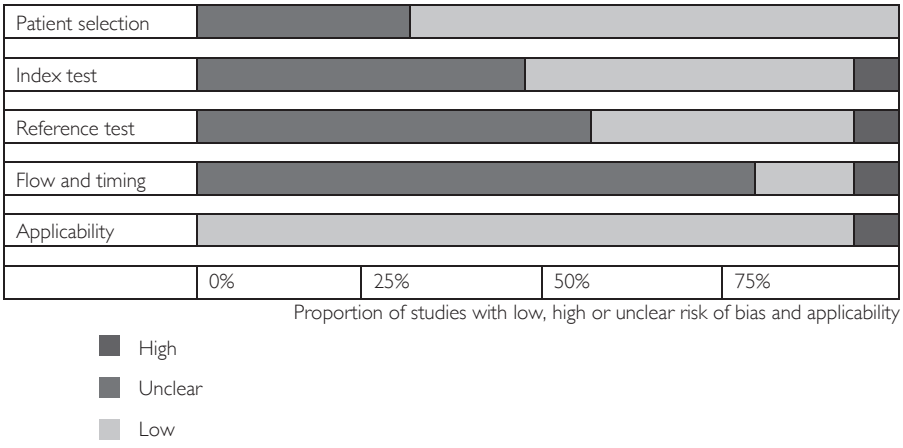
Table 2 presents quality assessment of the included studies.[12-24] Quality assessment showed in four studies (25%) a 'low' risk of bias on all four items, three studies showed a 'high' risk of bias on one of the items, while eight studies had an 'unclear' risk of bias on the description of methods on patient selection, the index or reference test. All studies, except for one scored 'low' on the three items of applicability.[12-23]

Based on a high concern of applicability of the index test and reference standard described in O'Connell et al, we decided to exclude this study.[24] After study selection and quality assessment, we included 12 articles in this systematic review, reporting on 1,029 women with postmenopausal bleeding (Table 1 and 2, Figure 2).

Table 2. Risk of bias and concerns of applicability by study using a modified Quadas-2 tool[11]

	Risk of bias				Applicability concerns		
	Patient selection	**Index test**	**Reference standard**	**Flow and timing**	**Patient selection**	**Index test**	**Reference standard**
Goldberg, '82	Unclear	Unclear	Unclear	Low	Low	Low	Low
Batool, '94	Unclear	Low	Low	Low	Low	Low	Low
Ben-Baruch, '94	Unclear	Unclear	Unclear	High	Low	Low	Low
vdBosch, '95	Low	High	Unclear	Low	Low	Low	Low
vdBosch '96	Low	Low	High	Low	Low	Low	Low
Giusa-Chifieri,'96	Unclear	Unclear	Unclear	High	Low	Low	Low
Gupta, '96	Low	Low	Low	Low	Low	Low	Low
De Silva '97	Low	Low	Low	Low	Low	Low	Low
Mortakis '97	Unclear	Unclear	Unclear	Low	Low	Low	Low
O'Connell '97	Unclear	Unclear	Unclear	Low	Low	High	High
Bunyavejchevin '01	Low	Low	Low	Low	Low	Low	Low
Epstein '01	Low	Low	Low	Low	Low	Low	Low
Spicer '06	Low	Unclear	Unclear	Unclear	Low	Low	Low

Figure 2. Overall risk of bias and applicability using a modified Quadas-2 tool.[11]



Diagnostic accuracy of endometrial sampling in women with PMB

Table 1 and 3 show the findings of the 12 included studies[12-23]. The Pipelle® device was used in eight studies,[12,13,15-17,20-22] while the other studies reported on the use of Accurette®,[23] Endorette®,[18] and Novak endometrial sampler®.[14] One study reported on two different sampling methods: Accurette® and Vabra®.[19]

Blind D&C was used as the reference standard in five studies[17-21] while hysteroscopy with histology (by biopsy and/or curettage) was the reference standard

in seven studies.[12-16,22,23] In three studies the diagnosis of endometrial cancer detected by endometrial sampling was confirmed by hysterectomy and not by hysteroscopy or D&C.[12,13,21]

All 12 studies reported on the fraction of women in whom endometrial sampling failed, mostly due to cervical stenosis. The failure rates of endometrial sampling varied between 1% and 53%, with a weighted failure rate of 11 %. Eight studies reported on the fraction of women in whom insufficient material was found at histology, which varied between 7% and 76%, with a weighted insufficient rate of 31 %.[14,16-21,23] In the article by Batool et al the rate of insufficient samples was much higher than in the other studies (42/55). In 37 of these women with an insufficient sample, material was also insufficient for diagnosis by D&C, which might explain the high insuffient-rate.[20]

The weighted percentage of women with endometrial (pre) cancer among those who had failed or insufficient sampling is 7% (range 0%-18% in seven studies). Goldberg et al described a percentage of 18% endometrial cancer in women with insufficient or failed samples. This article from 1982, lacked detail on the small number of women (n=12) included.[19]

Diagnosis of endometrial cancer

From all 12 articles we could extract data on the sensitivity and specificity regarding the diagnosis endometrial cancer (Table 3). The sensitivity of endometrial sampling was 100% in all five studies using blind D&C, but varied between 50-100% in the seven studies using hysteroscopy with histology as a reference standard, with a weighted sensitivity of 90%. Specificity was 99-100% regardless of the reference standard that was used. Figure 3A shows an ROC plot of the performance of the 12 studies that allowed the calculation of both sensitivity and specificity.

Diagnosis of (pre)cancer of the endometrium

With respect to the diagnosis of endometrial (pre-) cancer, i.e. atypical hyperplasia or endometrial cancer we could calculate sensitivity and specificity from the data in all five studies using D&C as a reference and in four studies using hysteroscopy as a reference (table 3). The weighted sensitivity in studies using D&C was 92% (range 71-100%), whereas the weighted sensitivity in studies using hysteroscopy as a reference standard was 82% (range 56-94%). Specificity was 99-100% in all studies. Figure 3B shows an ROC plot of the performance of the twelve studies that allowed the calculation of both sensitivity and specificity.

Table 3. Feasibility and diagnostic accuracy of endometrial sampling

				Endometrial cancer		Cancer or atypical hyperplasia		Endometrial disease	
Study and reference standard	**Failed samples n (%)**	**Insufficient samples n (%)**	**(pre)cancer in failed/ insufficient samples n (%)**	**+ test (sens)**	**- test (spec)**	**+ test (sens)**	**- test (spec)**	**+test (sens)**	**- test (spec)**
Blind D&C									
Goldberg, '82									
Accurette	5/40 (13)	7/35 (20)	2/12 (17)	3/3 (1.0)	25/25 (1.0)	8/9 (0.89)	19/19 (1.0)	nr	nr
Vabra	5/40 (13)	6/35 (17)	2/11 (18)	3/3 (1.0)	26/26 (1.0)	9/9 (1.0)	20/20 (1.0)	nr	nr
Batool, '94	15/70 (21)	42/55 (76)	0	3/3 (1.0)	8/8 (1.0)	nr	nr	0	0
Ben-Baruch, '94	2/90 (2)	6/88 (16)	0	9/9 (1.0)	36/36 (1.0)	10/10 (1.0)	35/35 (1.0)	0	0
Bunyavejchevin '01	16/30 (53)	7/14 (50)	1/23 (4)	2/2 (1.0)	5/5 (1.0)	2/2 (1.0)	5/5 (1.0)	nr	nr
Epstein '01	21/133 (16)	31/112 (28)	nr	nr	nr	5/7 (0.71)	nr (0.99)	10/31 (0.29)	nr (0.99)
Hysteroscopy									
vdBosch, '95	2/106 (2)	nr	0	5/5 (1.0)	80/80 (1.0)	nr	nr	20/39 (0.51)	43/43 (1.0)
vdBosch '96	2/140 (1)	nr	0	6/6 (1.0)	nr (0.99)	nr (0.64)	nr	nr (0.45)	nr (0.99)
Giusa-Chifieri,'96	8/80 (10)	6/72 (8)	1/14 (7)	16/17 (0.94)	49/49 (1.0)	17/18 (0.94)	48/48 (1.0)	nr	nr
Gupta, '96	22/76 (29)	nr	0	3/3 (1.0)	51/51 (1.0)	nr	nr	9/13 (0.69)	40/41(0.98)
De Silva '97	9/50 (18)	6/41 (15)	1/15 (7)	1/2 (0.5)	13/13 (1.0)	nr	nr	2/6 (0.33)	9/9 (1.0)
Mortakis '97	2/78 (3)	nr	1 (?)	5/6 (0.83)	70/70 (1.0)	8/11 (0.73)	65/65 (1.0)	9/43 (0.21)	33/33 (1.0)
Spicer '06	15/136 (11)	65/136 (48)	3/80 (4)	2/3 (0.67)	53/53 (1.0)	3/5 (0.56)	50/50 (1.0)	nr	nr

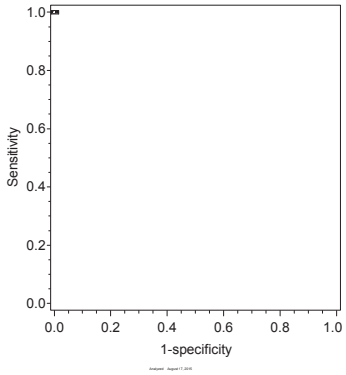
nr=not reported; sens = sensitivity; spec = specificity; endometrial disease = polyp/hyperplasia/cancer; *for total number of studies

Diagnosis of endometrial disease

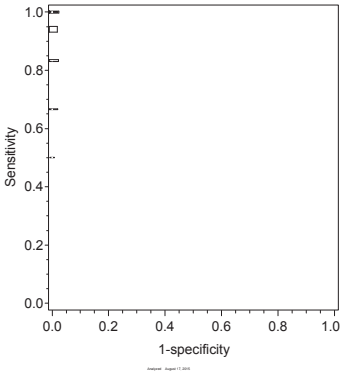
As in most studies diagnostic accuracy regarding benign pathology was not described separately, we decided to extract data on the accuracy regarding the diagnosis of endometrial disease, i.e. endometrial cancer, hyperplasia and endometrial polyps together (table 3). The sensitivity of endometrial sampling was 29% in one study using blind D&C and the weighted sensitivity was 39% (range 21-69%) in five studies using hysteroscopy with histology as a reference standard. Specificity was again high, 98-100% regardless of the reference standard used. Figure 3C shows an ROC plot of the performance of the twelve studies that allowed the calculation of both sensitivity and specificity.

Figure 3A1 tm 3C2. Receiver operating curve (ROC) plots demonstrating the accuracy of endometrial sampling in diagnosing endometrial cancer, endometrial (pre) cancer or endometrial disease with D&C or hysteroscopy as a reference standard

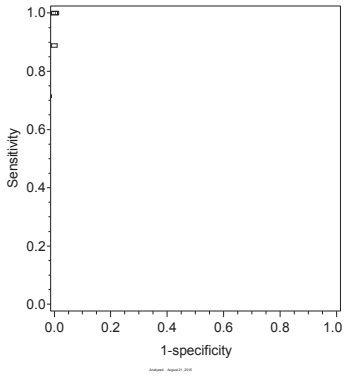
A1. ROC plot for endometrial cancer with D&C as reference



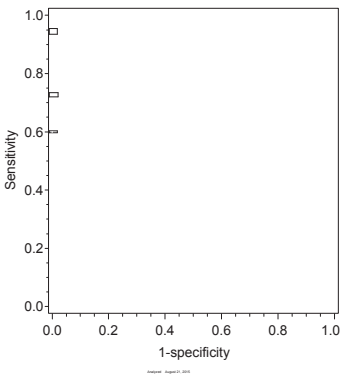
A2. ROC plot for endometrial cancer with hysteroscopy as a reference



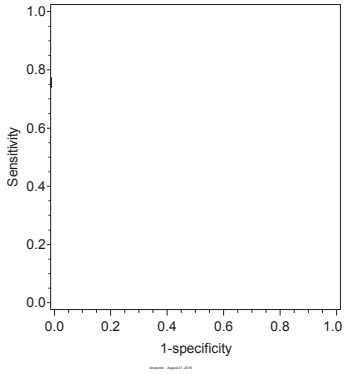
B1. ROC plot for endometrial (pre) cancer with D&C as reference



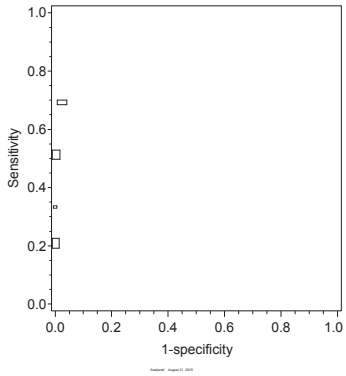
B2. ROC plot for endometrial (pre) cancer with hysteroscopy as a reference



C1. ROC plot for endometrial disease with D&C as a reference



C2. ROC plot for endometrial disease with hysteroscopy as a reference



Discussion

In this meta-analysis, we assessed the diagnostic accuracy of endometrial sampling regarding the diagnoses of endometrial cancer, endometrial (pre) cancer and endometrial disease (including endometrial polyps) in women with PMB, compared to two different reference strategies: D&C and hysteroscopy. Specificity of endometrial sampling is very high, irrespective of the type of disease or the reference test that was used. Sensitivities, on the other hand, are lower than anticipated based on existing meta-analyses, for all types of disease, but especially for atypical hyperplasia and endometrial disease, which includes endometrial polyps.

An important strength of this meta-analysis is that we performed a thorough search for articles on the diagnostic accuracy in women with PMB. By searching with all synonyms for PMB and endometrial sampling, we think we selected all articles on this subject. We also selected articles, which described only a subgroup of postmenopausal women and tried to contact the authors of these articles. Unfortunately, none of them responded. We included all eligible articles, regardless of the language used.

This article also has several limitations. Publication bias and the risk of missing potentially relevant articles are concerns with any systematic review. We attempted to mitigate this issue by using a robust search strategy, by checking cross-references and by consulting with a clinical librarian. Also, observer agreement regarding study selection was high. However, by performing this rigorous systematic search, we

could only identify four more studies compared to the three existing meta-analyses on this subject.[7-9]

Another weakness is that, because only a small number of studies is available and most studies are based on small samples, we had to draw conclusions based on a limited number of patients. Apart from the limited power, the relatively small number of studies and variability in methods also did not allow for more standard statistical analyses recommended for diagnostic test accuracy reviews, such as pooling sensitivity and specificity using the bivariate model or estimating summary ROCs.

The three existing meta-analyses focused on the diagnostic accuracy of endometrial sampling in a mixed population of pre- and postmenopausal women.[7-9] As the diagnostic accuracy of a test is strongly dependent on the prevalence (or pre-test probability) of a diagnosis, and the prevalence of endometrial cancer and atypical hyperplasia is much lower in pre- versus postmenopausal women, we think it is important to study this subject in a selected population of women with PMB. Therefore, we searched specifically for articles on the diagnostic accuracy of endometrial sampling in women with PMB and included only these studies, which reported data on postmenopausal bleeding separately.

Endometrial sampling fails in 42% of cases (either technical failure or insuffient material) and in 7% of these cases a (pre)cancer is found. This finding is in accordance with findings in other studies, which describe a failure or inconclusive rate of 16% to 50 % and in 5 to 20 % of these cases significant endometrial pathology is found.[25-27] Therefore, a case of a failed or inconclusive sample, should lead to further diagnostic work-up. Also, a benign result of endometrial sampling is not completely reassuring, as sensitivities are lower than anticipated based on previous literature. In the three existing meta-analyses (blind) D&C has been used as a reference standard, which is worrisome as D&C is known to miss 50-85% of focal intracavitary pathology.[28,29] As D&C could miss focal pathology, it could also possibly miss endometrial (pre) cancer in an endometrial polyp. Therefore, nowadays, D&C is almost completely replaced by hysteroscopy as a reference standard, both in clinical as well as in research settings.[10] It suggests that endometrial sampling, which is performed as a mini-curettage, as well misses a significant number of focal pathologies and therefore possibly also focal (pre) cancers. Because in women with atypical hyperplasia (which is regarded as endometrial (pre) cancer in 17-52% an underlying cancer is found at hysterectomy,[30] it is important to diagnose not only endometrial cancer but also atypical hyperplasia. Given the above findings,

further diagnostic work-up for focal intracavitary pathology in women with a failed, insufficient or benign result of endometrial sampling seems warranted.

The results of this systematic review suggest that the sensitivity of endometrial sampling is lower than was thought before for all types of disease, but especially for the diagnosis of atypical hyperplasia and endometrial disease in general. The question is if we can reassure patients without an endometrial polyp and a benign result of endometrial sampling. Is sensitivity of endometrial sampling especially low in women with an endometrial polyp? Unfortunately, we cannot answer these questions based on available literature. Therefore, more research on this subject is needed, using larger samples, given the prevalence of endometrial cancer and atypical hyperplasia (5-10%). Future research should therefore aim to gather information about large (prospective) cohorts of patients with PMB, to study the (cost-)effectiveness and diagnostic accuracy of the endometrial biopsy and hysteroscopy in the diagnostic pathway in women with PMB and a thickened endometrium on TVS.

Appendix

#	Searches
1	uterine hemorrhage/ or metrorrhagia/
2	((uterine or vaginal or abnormal) adj3 (h?emorrhage or metrorrhagia or bleeding)).ti,ab.
3	1 or 2
4	Postmenopause/
5	(postmenopaus* or post-menopaus*).ti,ab.
6	4 or 5
7	3 and 6
8	endometrial sampling*.ti,ab,kw.
9	pipelle*.ti,ab.
10	((biop* or sample* or aspiration) adj3 of endometri*).ti,ab,kw.
11	endometri* biop*.ti,ab,kw.
12	Biopsy/ and exp Endometrium/
13	8 or 9 or 10 or 11 or 12
14	7 and 13
15	exp "Sensitivity and Specificity"/
16	(Sensitiv* or Specific*).ti,ab.
17	(predict or ROC-curve or receiver-operator*).ti,ab.
18	(likelihood or LR*).ti,ab.
19	exp Diagnostic Errors/
20	(inter-observer or intra-observer or interobserver or intraobserver or validity or kappa or reliability).ti,ab.
21	reproducibility.ti,ab.
22	(test adj2 (re-test or retest)).ti,ab.
23	"Reproducibility of Results"/
24	accuracy.ti,ab.
25	Diagnosis, Differential/
26	validation studies.pt.
27	(failure* or success* or inadequate* or inconclusive*).ti,ab.
28	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29	14 and 28

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Chapter 8

Summary
In English and Dutch

Summary

This thesis studied the diagnostic work-up of women with postmenopausal bleeding (PMB): vaginal bleeding that occurs after a period of 12 months without menstruation at the menopausal age. This chapter summarises the findings of the research we conducted.

Chapter 1 outlines the theoretical background and description of the problem studied in this thesis. Endometrial cancer is defined as cancer from the lining or inside of the uterus (endometrium), and is linked to older age and obesity. As people are living longer and the prevalence of obesity is rising, the incidence of endometrial cancer or pre-cancer (atypical hyperplasia) is expected to rise in the upcoming decades.

In 95% of women, endometrial cancer presents with PMB, mostly at an early stage when curative treatment is still possible. It is therefore considered important to investigate all women who present with PMB. However, only 10% of women with PMB have an underlying diagnosis of endometrial cancer and the most frequent findings are endometrial polyps. Although only sparse evidence is available on this, polyps are believed to be responsible for recurrent bleeding. Consequently, the removal of endometrial polyps is the subject of debate and research.

Diagnostic work-up in women with PMB thus focuses on *both* the exclusion of endometrial cancer and on the (possible) diagnosis and treatment of endometrial polyps. This thesis studied these two aspects by investigating six research questions. The six research questions and the research conducted in this thesis are explained below.

1. What is already known in the literature about the diagnostic work-up in women with PMB?

Chapter 2 summarises the existing systematic reviews on this subject and provides an overview of different diagnostic tools. Four types of diagnostic tests are described: measurement of endometrial thickness by transvaginal ultrasound (TVS), endometrial sampling (an outpatient biopsy of the lining of the uterus), saline infusion sonography (SIS, an ultrasound in which water or gel installation is used to better visualize the inside of the uterus) and hysteroscopy (inspection of the inside of the uterus with a small camera). All four tests have shown to independently rule out endometrial

cancer. However, there is no consensus in systematic reviews or in international guidelines about the sequence in which these methods should be employed in women with PMB.

2. Which different prediction models on the chance of endometrial cancer in women with PMB are available in literature and which model shows the best performance?

In **Chapter 3**, we systematically reviewed the literature to map the prediction models available on this subject and to identify their performance in internal validation. It would be useful to identify women who display a high risk of having endometrial cancer based not only on the measurement of endometrial thickness but also on the patient's characteristics. Many researchers have studied this subject and have developed prediction models consisting of different predictor variables. We identified nine prognostic studies, of which we assessed the quality, the different phases of development and their performance. The nine articles investigated 27 different possible predictor variables. It was found that the most important patient characteristics are age, body mass index, diabetes, frequency of bleeding, use of anticoagulants and hormones. Endometrial thickness, endometrial morphology and endometrial border were identified as significant ultrasound variables. In the three articles studying the use of Doppler for predicting endometrial cancer, endometrial colour score and vascularity index were identified as the most important predictor variables. None of the detected models completed external validation or impact analysis. Models including power Doppler showed the best performance in internal validation, but Doppler is not easily accessible in general gynaecological practice. We can conclude that the first step in the approach of women with postmenopausal bleeding should be to distinguish between women with low risk versus high risk of having endometrial carcinoma based on patient's characteristics.

3. Is a prediction model based on patient characteristics useful in daily practice to differentiate between women with a high and a low risk of endometrial cancer?

External validation of a prediction model is the first step towards implementing the model in clinical practice. In **Chapter 4** we externally validated a mathematical model, which is based on patient characteristics with or without TVS. We retrospectively

evaluated two previously developed prediction models in two independent datasets of women with PMB: one Dutch dataset (559 women) and one Swedish dataset (433 women). We also evaluated three diagnostic strategies:

- a 'patient characteristics' rule, based on characteristics of the women without TVS;
- a 'sequential' rule, i.e. TVS in case the probability for cancer exceeded 4% based on characteristic, and subsequent endometrial sampling when the endometrial thickness exceeded 4 mm;
- an 'integrated' rule with a probability estimate based on both characteristics of the women and ultrasound results and endometrial sampling when the probability of cancer exceeded 4%.

In both the Dutch and the Swedish databases, the two models showed good performance in terms of discrimination and calibration. Based on these two models, each of the three strategies detected all women with endometrial (pre) cancer. Applying the 'integrated' or 'sequential' strategy would, compared to current practice (ultrasound only), lead to a 7% decrease in the number of women in need of further invasive testing. Thus, the use of a prediction model based on 'patient characteristic and ultrasound' factors in a sequential or integrated strategy, could only slightly reduce the number of invasive procedures without loss in detection of endometrial cancer.

4. Is the diagnostic work-up for and the removal of benign endometrial polyps effective in women with PMB to prevent recurrent bleeding?

Chapter 5 presents the results of a multicentre, randomised controlled trial on the effectiveness of hysteroscopic diagnosis and treatment of endometrial polyps versus expectant management in women with PMB, a thickened endometrium and benign endometrial sampling. We randomised 98 women for diagnostic work-up by hysteroscopy (preceded by SIS) versus 102 women for expectant management. The primary outcome measure was the recurrence of PMB within a year after randomisation. Pathology results were registered as well. Results show that within one year a total of 15 women (15.3%) in the hysteroscopy group experienced recurrent bleeding, versus 18 (18.0%) in the expectant management group (relative risk 0.85 (95% CI 0.46-1.59)). In the hysteroscopy group, we found 50 (51%) polyps

at initial hysteroscopy. In these 50 polyps, the pathology results showed six (pre) cancers (6%). From this trial we can conclude that in women with PMB, a thickened endometrium and benign endometrial sampling, operative hysteroscopy does not reduce recurrent bleeding. Yet, hysteroscopy detected focal endometrial (pre) cancer in 6% of women who had benign endometrial sampling. This finding indicates that in these women, further diagnostic work-up is warranted to detect focal (pre) cancers missed by endometrial sampling.

5. Is the diagnostic work-up for and the removal of benign endometrial polyps cost-effective in women with PMB?

Results of the cost-effectiveness analysis performed alongside the above-described randomised trial are presented in **Chapter 6**. Outcomes for the cost-effectiveness analysis (CEA) were cost-differences for the two randomisation-groups and incremental cost-effectiveness ratios for the prevention of recurrent bleeding and detection of endometrial (pre) cancers. Statistically, the results show that costs in the intervention group were significantly higher compared to the expectant management group (cost difference 780 euro (95% 550; 1158)), however the effect difference in the number of women with recurrent bleeding was not significantly different between the two groups (-3% (95% CI -13; 8%)). The CEA for the detection of endometrial (pre) cancers showed both a statistically significant effect difference (7% (95% CI 3; 14%)) and a statistically significant cost difference (780 euro (95% 550; 1158)). To detect one case of (pre) cancer, 10,917 euro should be invested in the hysteroscopy group as compared with the expectant management group. These costs can be lowered to 8,913 euro if a strategy that uses SIS to select women for hysteroscopy is employed. In women with PMB (a thickened endometrium and benign endometrial sampling) operative hysteroscopy does not reduce recurrent bleeding, however hysteroscopy detected focal endometrial (pre) cancer in 6% of these women. A strategy using hysteroscopy in all women with a thickened endometrium and benign endometrial sampling is about 2000 euro more expensive per patient than a strategy using SIS to select women for therapeutic hysteroscopy to detect endometrial (pre) cancers.

6. Is the diagnostic accuracy of outpatient endometrial sampling as high as we thought based on previous literature?

Chapter 7 presents the results of the last researched subject of this thesis: a systematic review and meta-analysis on the diagnostic accuracy of endometrial sampling for the diagnoses of endometrial cancer, atypical hyperplasia and endometrial disease (endometrial pathology, including benign polyps). We identified 12 studies comparing the results of endometrial sampling with two different reference standards: five studies on blind dilatation and curettage and seven studies on hysteroscopy with histology. 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 assessed the diagnostic accuracy of endometrial sampling and found that specificity of endometrial sampling is very high, irrespective of the type of disease or the reference test that was used. Sensitivity, on the other hand, is lower than previously thought based on existing meta-analyses, for all types of disease, but especially for atypical hyperplasia and endometrial disease, which includes endometrial polyps. From this meta-analysis we can conclude that in cases of 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.

Nederlandse samenvatting

In dit proefschrift onderzoeken we de diagnostische strategieën die worden gebruikt bij vrouwen die zich presenteren met postmenopauzaal bloedverlies: vaginaal bloedverlies dat later dan één jaar na de laatste menstruatie (de menopauze) optreedt. Dit hoofdstuk bevat de Nederlandse samenvatting van de bevindingen van het onderzoek dat we hebben uitgevoerd.

In **Hoofdstuk 1** van dit proefschrift wordt dieper ingegaan op de theoretische achtergrond en geven we een omschrijving van het probleem dat in dit proefschrift wordt onderzocht. Baarmoederkanker (of endometriumcarcinoom) is kanker die ontstaat in de binnenbekleding of het slijmvlies van de baarmoeder (het endometrium). Risicofactoren voor het krijgen van deze vorm van kanker zijn onder andere een hogere leeftijd en obesitas. Aangezien mensen steeds langer leven en de prevalentie van obesitas toeneemt, zal de incidentie van baarmoederkanker of van een voorstadium van baarmoederkanker (atypische hyperplasie) de komende decennia naar verwachting alleen maar toenemen.

Bij 95% van de vrouwen gaat baarmoederkanker gepaard met postmenopauzaal bloedverlies. Dit bloedverlies manifesteert zich vaak al in een vroeg stadium van de ziekte, wanneer een curatieve behandeling nog mogelijk is. Het wordt daarom van groot belang geacht om alle vrouwen met postmenopauzaal bloedverlies nader te onderzoeken. Slechts 10% van de vrouwen met postmenopauzaal bloedverlies heeft na onderzoek een onderliggende diagnose van baarmoederkanker. Veel vaker blijkt sprake te zijn van een (goedaardige) endometriumpoliep. Hoewel er op dit moment nog weinig goed onderzoek beschikbaar is, denkt men dat poliepen de oorzaak zijn van de terugkerende bloedingen. Om die reden vormt de verwijdering van de endometriumpoliepen een onderwerp van discussie en onderzoek.

De diagnostische strategieën bij vrouwen met postmenopauzaal bloedverlies richten zich *zowel* op het diagnosticeren en uitsluiten van baarmoederkanker *als* op de (eventuele) diagnose en behandeling van endometriumpoliepen. In dit proefschrift bestuderen we deze twee aspecten door in te gaan op zes onderzoeksvragen. De zes onderzoeksvragen en het in dit proefschrift uitgevoerde onderzoek worden hieronder nader toegelicht.

1. Wat is in de literatuur al bekend over de diagnostische strategieën bij vrouwen met postmenopauzaal bloedverlies?

In **Hoofdstuk 2** vindt u een samenvatting van de bestaande systematische reviews op dit gebied en een overzicht van de verschillende diagnostische middelen. Er worden vier soorten diagnostische onderzoeken beschreven: meting van de dikte van het endometrium met een transvaginale echografie, een endometriumbiopt (poliklinisch wegnemen van een stukje baarmoederslijmvlies), een watercontrastecho (SIS, een echografie waarbij water of gel wordt ingespoten om de binnenkant van de baarmoeder beter in beeld te brengen) en hysteroscopie (onderzoek van de binnenkant van de baarmoeder met een kleine camera). Alle vier de onderzoeken blijken los van elkaar baarmoederkanker redelijk betrouwbaar uit te kunnen sluiten. Er bestaat in systematische reviews en internationale richtlijnen echter geen consensus over de volgorde waarin deze methoden zouden moeten worden ingezet bij vrouwen met postmenopauzaal bloedverlies.

2. Welke verschillende predictiemodellen over de kans op baarmoederkanker bij vrouwen met postmenopauzaal bloedverlies zijn in de literatuur beschikbaar en welk model levert de beste resultaten op?

In **Hoofdstuk 3** deden we systematisch literatuuronderzoek om de over dit onderwerp beschikbare predictiemodellen in kaart te brengen en te kijken hoe deze modellen presteren op het gebied van interne validatie. Het zou nuttig kunnen zijn om de vrouwen met een verhoogd risico op baarmoederkanker te kunnen selecteren op basis van zowel de meting van de endometriumdikte, als op basis van de patiëntkenmerken. Dit onderwerp is reeds door een groot aantal onderzoekers onderzocht en zij hebben predictiemodellen ontwikkeld die uit verschillende voorspellende variabelen bestaan. Wij onderzochten negen studies waarin deze modellen ontwikkeld zijn en beoordeelden de kwaliteit, de verschillende ontwikkelingsfasen en de resultaten van deze modellen. In de negen artikelen werden 27 verschillende mogelijke voorspellende variabelen onderzocht. De belangrijkste patiëntkenmerken zijn: leeftijd, BMI, diabetes, bloedingsfrequentie en gebruik van antistollingsmiddelen en het gebruik van hormonen. De endometriumdikte, de endometriummorfologie (hoe ziet het eruit) en de endometrium-grens werden aangemerkt als significante echografische variabelen. In de drie artikelen die de toepassing van Dopplerondersoek onderzochten om baarmoederkanker te

herkennen, werden de Doppler kleurenscore en de vascullariteitsindex als de belangrijkste voorspellende variabelen aangemerkt. In geen van de gevonden modellen werd een externe validatie of impactanalyse uitgevoerd. De modellen met power Doppler lieten de beste prestaties op het gebied van interne validatie zien, maar Doppler is in de algemene gynaecologische praktijk (nog) niet altijd heel makkelijk beschikbaar. We kunnen concluderen dat de eerste stap in de diagnostische strategie bij vrouwen met postmenopauzaal bloedverlies moet zijn dat er op basis van patiëntkenmerken een onderscheid moet worden gemaakt tussen vrouwen met een laag risico en vrouwen met een hoog risico op baarmoederkanker.

3. Zou een predictiemodel op basis van patiëntkenmerken in de dagelijkse praktijk nuttig kunnen zijn om het onderscheid te maken tussen vrouwen met een hoog en vrouwen met een laag risico op baarmoederkanker?

Externe validatie van een predictiemodel is de eerste stap naar de invoering van een dergelijk model in de klinische praktijk. In **Hoofdstuk 4** hebben we een wiskundig model dat is gebaseerd op patiëntkenmerken, met of zonder echoscopie, extern gevalideerd. We hebben twee eerder ontwikkelde predictiemodellen retrospectief beoordeeld in twee onafhankelijke datasets met vrouwen met postmenopauzaal bloedverlies: één Nederlandse dataset (559 vrouwen) en één Zweedse dataset (433 vrouwen). Daarnaast hebben we drie diagnostische strategieën geëvalueerd:

- een 'patiëntkenmerken'-strategie op basis van de kenmerken van de vrouwen zonder meting van de endometriumdikte;
- een 'sequentiële' strategie, d.w.z. echoscopische meting van de endometriumdikte wanneer de kans op kanker hoger is dan 4% op basis van de kenmerken, en een daarop volgend endometriumbiopt als het endometrium dikker is dan 4 mm;
- en een 'geïntegreerde' strategie: met een kans inschatting die is gebaseerd op zowel de patiëntkenmerken als de resultaten van de echografie, en een endometriumbiopt wanneer de kans op kanker groter is dan 4%.

In zowel de Nederlandse als de Zweedse datasets presteerden de twee modellen goed op het gebied van discriminatie en kalibratie. Op basis van deze twee modellen detecteerde elk van de drie strategieën alle vrouwen met (een voorstadium van) baarmoederkanker. Toepassing van de 'geïntegreerde' of 'sequentiële' strategie zou er,

in vergelijking met de huidige praktijk (alleen echografie), toe leiden dat het aantal vrouwen dat invasieve vervolgonderzoeken moet ondergaan met 7% daalt. Dus, als we gebruikmaken van een predictiemodel op basis van 'patiëntkenmerken en echografie' in een sequentiële of geïntegreerde strategie, kan het aantal invasieve ingrepen slechts minimaal worden teruggebracht, zonder detectieverlies van baarmoederkanker.

7. Zijn de diagnostische strategieën voor benigne endometriumpoliepen en de verwijdering daarvan bij vrouwen met postmenopauzaal bloedverlies effectief om terugkerend bloedverlies te voorkomen?

In **Hoofdstuk 5** presenteren we de resultaten van een multicentrische, gerandomiseerde, gecontroleerde trial naar de effectiviteit van een diagnostische en therapeutische hysteroscopie van endometriumpoliepen versus een afwachtend beleid bij vrouwen met postmenopauzaal bloedverlies, een verdikt endometrium en een goede uitslag van het endometriumbiopt. We randomiseerden 98 vrouwen voor een diagnostische hysteroscopie (voorafgegaan door SIS) versus 102 vrouwen voor een afwachtend beleid. De primaire uitkomstmaat was recidiverend bloedverlies binnen een jaar na randomisatie. Ook de resultaten van het pathologisch onderzoek werden geregistreerd. Uit de resultaten bleek dat binnen één jaar in totaal 15 vrouwen (15,3%) in de hysteroscopiegroep last hadden van recidiverend bloedverlies, versus 18 vrouwen (18,0%) in de groep met het afwachtende beleid (relatief risico 0,85 (95% BI 0,46-1,59)). In de hysteroscopiegroep vonden we 50 (51%) poliepen bij de aanvankelijke hysteroscopie. In deze 50 poliepen werden in het pathologisch onderzoek zes (pre) kankers (6%) gevonden. Op basis van deze trial kunnen we concluderen dat de kans op recidiverend bloedverlies bij vrouwen met postmenopauzaal bloedverlies, een verdikt endometrium en een goede uitslag van het endometriumbiopt, door operatieve hysteroscopie niet afneemt. Toch werd er dankzij de hysteroscopie bij 6% van de vrouwen met een goede uitslag van het endometriumbiopt (een voorstadium van) baarmoederkanker ontdekt. Deze bevinding geeft aan dat bij deze vrouwen verdere diagnostische strategieën toegepast moeten worden om (pre-)kankers te detecteren die door het endometriumbiopt gemist worden.

8. Zijn de diagnostische strategieën voor benigne endometriumpoliepen en de verwijdering daarvan bij vrouwen met postmenopauzaal bloedverlies kosteneffectief?

De resultaten van de kosteneffectiviteitsanalyse die naast de hierboven beschreven gerandomiseerde trial werd uitgevoerd, staan beschreven in **Hoofdstuk 6**. De primaire uitkomstmaten van de kosteneffectiviteitsanalyse (KEA) waren kostenverschillen voor de twee gerandomiseerde groepen en incrementele kosteneffectiviteitsratio's voor de preventie van terugkerend bloedverlies en de detectie van (voorstadia van) baarmoederkanker. Statistisch gezien tonen de resultaten aan dat de kosten in de interventiegroep significant hoger waren dan die in de groep met het afwachtende beleid (kostenverschil van 780 euro (95% 550; 1158)). Het effectverschil in het aantal vrouwen met terugkerend bloedverlies was tussen de twee groepen echter niet significant anders (-3% (95% BI - 13; 8%)). De KEA voor de detectie van (voorstadia van) baarmoederkanker toonde zowel een statistisch significant effectverschil (7% (95% BI 3; 14%)) als een statistisch significant kostenverschil (780 euro (95% 550; 1158)) aan. Om één geval van (pre-)kanker op te sporen, moest er 10.917 euro worden geïnvesteerd in de hysteroscopiegroep in vergelijking met de groep met het afwachtende beleid. Deze kosten kunnen worden verlaagd tot 8.913 euro als er een strategie wordt gebruikt met SIS om de vrouwen te selecteren bij wie een hysteroscopie wordt gedaan. Bij vrouwen met postmenopauzaal bloedverlies (een verdikt endometrium en een goede uitslag van het endometriumbiopt) leidt operatieve hysteroscopie niet tot een afname van recidief bloedverlies, maar de hysteroscopie leidde bij 6% van deze vrouwen wel tot de detectie van (voorstadia van) baarmoederkanker. Een strategie waarbij hysteroscopie wordt gebruikt bij alle vrouwen met een verdikt endometrium en een goede uitslag van het endometriumbiopt kost ongeveer 2.000 euro per patiënt meer dan een strategie waarbij SIS wordt toegepast om de vrouwen te selecteren die voor therapeutische hysteroscopie in aanmerking komen om (voorstadia van) baarmoederkanker te detecteren.

9. Is de diagnostische nauwkeurigheid van een poliklinisch endometriumbiopt zo groot als we dachten op basis van de eerdere literatuur?

In **Hoofdstuk 7** worden de resultaten gepresenteerd van het laatst onderzochte onderwerp van dit proefschrift: een systematische review en meta-analyse van de diagnostische nauwkeurigheid van endometriumbiopten voor de diagnose van baarmoederkanker, atypische hyperplasie en endometriumafwijkingen (endometriumpathologie, waaronder goedaardige poliepen). We hebben 12 studies bekeken die de resultaten van endometriumbiopten vergeleken met twee

verschillende referentiestandaarden: vijf studies inzake blinde curettage en zeven studies inzake hysteroscopie en histologisch onderzoek. Voor elke geïncludeerde studie berekenden we het percentage vrouwen bij wie het endometriumbiopt faalde. Bovendien extraheerden we de gevallen van baarmoederkanker, atypische hyperplasie en endometriumafwijkingen die door het endometriumbiopt waren ontdekt of over het hoofd waren gezien. We beoordeelden de diagnostische nauwkeurigheid van het endometriumbiopt en ontdekten dat de specificiteit van het endometriumbiopt zeer hoog was, ongeacht de aard van de afwijking of de referentietest die werd gebruikt. De sensitiviteit was echter lager dan aanvankelijk werd aangenomen op basis van bestaande meta-analyses. Dit geldt voor alle soorten afwijkingen, maar met name voor atypische hyperplasie en endometriumafwijkingen, waaronder endometriumpoliepen. Op basis van deze meta-analyse kunnen we concluderen dat bij vrouwen met postmenopauzaal bloedverlies, de sensitiviteit van een endometriumbiopt om baarmoederkanker, en met name atypische hyperplasie en endometriumafwijkingen, zoals endometriumpoliepen, te detecteren, lager is dan eerder werd aangenomen.

Chapter 9

General discussion and implications

General discussion

The work-up of women with postmenopausal bleeding focuses on the exclusion of endometrial (pre) cancers and (possible) diagnosis and treatment of endometrial polyps and can be divided in different stages:

1. Selecting women with a high risk of having endometrial cancer for further diagnostic work-up, by TVS, applying prediction models or adding Doppler features.
2. Invasive diagnostic work-up by endometrial sampling, SIS and/or hysteroscopy.
3. Treatment of women with (recurrent) PMB to prevent recurrent bleeding.

The selection of women with a high risk of endometrial cancer

When a patient presents with PMB the first step in most guidelines is referral to a gynaecologic practice for (vaginal) examination, Pap smear and TVS. Measurement of the endometrial thickness by TVS is an evidence-based method to distinguish between women with a low or high risk of having endometrial cancer. The measurement of endometrial thickness is easy to learn and the inter-observer variability is very low.[1] This method is well studied and widely implemented.[2-4] It has shown to be accurate in ruling out endometrial cancer, with a risk of endometrial cancer when the test is negative of 0.7–3.5%, depending on the cut-off point used (Chapter 2).

The risk after a negative test (post-test probability) is not only dependent on test characteristics, but also on the pre-test probability, which is altered by patient characteristics. To lower the post-test probability, patient characteristics could be implemented in the diagnostic work-up by implementing prediction models. However, the use of these models is not thoroughly studied and until now only one of the models has been externally validated (Chapter 3 and 4). Therefore, implementation of prediction models in clinical practice is still not possible. The external validation of a model developed by Opmeer et al showed that in situations where no ultrasound is available, women could safely be selected based on their characteristics. However, this is only the case for a very low specificity, which means that many women need to undergo further invasive testing with a small chance of diagnosing a (pre) cancer. In the Dutch case, all gynaecologist have easy access to an ultrasound machine, which instigates that this model is not applicable in the Dutch healthcare system. A model based on patient characteristics would only be useful if the number of invasive procedures could be significantly decreased. By combining patient characteristics

in a prediction model with TVS, the number of women that need further invasive procedures to obtain material for histological assessment can be decreased only slightly, compared to the measurement of endometrial thickness by TVS (Chapter 4). Therefore, this model is also currently not ready to be used in clinical practice.

Invasive diagnostic work-up

When a thickened endometrium is diagnosed in women with PMB, further invasive work-up is indicated because of a high risk of having endometrial (pre) cancer. In most guidelines, TVS will be followed by endometrial sampling to obtain histology. Nowadays, hysteroscopy is often used as the next step after endometrial sampling in the diagnostic work-up, but could also be seen as an alternative to endometrial sampling with the advantage of diagnosing and directly removing an endometrial polyp. Although hysteroscopic polypectomy is one of the most frequently performed procedures in gynaecologic practice, the causative relationship between endometrial polyps and (postmenopausal) recurrent bleeding is not proven. In postmenopausal women with a thickened endometrium, only one cohort study is available and this study shows no difference in recurrent bleeding after hysteroscopy versus expectant management, regardless if a polyp was present or not.[5] From our randomised trial we can conclude that operative hysteroscopy does not reduce recurrent bleeding and that costs to prevent one case of recurrent bleeding are quite high (around 29,000 euro). Yet, hysteroscopy detected focal endometrial (pre) cancer in 6% of women was initially missed by endometrial sampling (Chapter 5 and 6). This finding, together with the fact that sensitivity of endometrial sampling is much lower than we thought (Chapter 7), warrants further diagnostic work-up in women with a thickened endometrium and benign histology to diagnose focal endometrial (pre) cancers. Furthermore, endometrial sampling fails in about 40% of cases (because either it is not performed successfully or shows an insufficient sample) and in about 7% of these failed samples an endometrial (pre) cancer is diagnosed. In combination, these findings make us question whether endometrial sampling should still be part of the diagnostic work-up of women with PMB.

Such a diagnostic work-up to diagnose focal endometrial (pre) cancers could involve a strategy with direct hysteroscopy in all women or a strategy with SIS to select women for hysteroscopy with a (high suspicion of) an endometrial polyp. The cost-effectiveness analysis alongside our randomised trial shows that a strategy using SIS to select women for therapeutic hysteroscopy is about 2000-3000 euro less expensive per (pre) cancer detected compared to direct hysteroscopy for all

women. The possible 3000euro decrease in detecting one endometrial (pre) cancer could be an argument for implementing SIS in the diagnostic work-up. However, these costs are calculated for a setting in a Dutch hospital without the availability of a 'one-stop'-treatment and therefore these findings cannot be unconditionally generalised for all circumstances.

From current literature, it is unclear whether the diagnostic accuracy of SIS is high enough to select women for therapeutic hysteroscopy. From studies in premenopausal women we know that sensitivity of SIS to detect an abnormal uterine cavity is 95%.[6] We found a sensitivity of 93% and a specificity of 94% for SIS to diagnose endometrial polyps in postmenopausal women (Chapter 5). However, SIS currently cannot be implemented as a standard in guidelines on the diagnostic work-up of women with postmenopausal bleeding, because research on the diagnostic accuracy specifically in postmenopausal women is needed.

Prevention and treatment of recurrent bleeding

The idea behind the design of the randomised trial described in this thesis was that we sought to study the effectiveness of the removal of endometrial polyps on recurrent bleeding. From the results of this study we can conclude that diagnosing focal (pre) cancers should be the indication to perform a hysteroscopy and not the prevention of recurrent bleeding. In the literature, only sparse evidence is available on the prevalence of recurrent bleeding in women who present with PMB. In a Dutch cohort of women with PMB in whom previous investigations have yielded normal findings, the chance of recurrent bleeding was 10% for women with endometrial thickness < 4 millimetres and 21% with endometrial thickness ≥ 4 millimetres.[5,7] A British study showed a recurrent bleeding rate of 5% in a population of women with PMB and normal findings at initial investigation, regardless of the endometrial thickness.[8]

As the majority of women with recurrent PMB will not have a (pre)cancer, we do not have an effective treatment available for women with recurrent bleeding or an initial episode of PMB to prevent them from returning to the hospital with recurrent bleeding and undergo invasive diagnostic work-up. Women are often diagnosed with "atrophic endometrium" in cases where they present recurrent PMB, a thin endometrium (< 4 mm) and no abnormalities at hysteroscopy. On theoretical grounds, the use of local vaginal oestrogen therapy could prevent recurrent bleeding in women with postmenopausal bleeding caused by 'atrophy'. For women with initial endometrial thickness > 4 mm and negative hysteroscopy, insertion of LNG-IUD

has been described to have a beneficial effect with respect to recurrent PMB.[9] Furthermore, after LNG-IUD insertion, histological regression of hyperplasia is seen.[10,11] Given the burden of recurrent PMB for patients and the burden of repeated hysteroscopies, there is a need to establish a safe and effective intervention for women with (recurrent) PMB to prevent recurrent bleeding.

Future research

The selection of women with a high risk of endometrial cancer

The use of prediction models in women who present with PMB should be studied further. Existing models could be adjusted with different thresholds (for example a different threshold for the endometrial thickness) or by the use of different subgroups of patients. It would be useful to implement such a model in clinical practice only if the number of invasive procedures can be reduced without missing endometrial cancers. Furthermore, research should focus on the use of Doppler. Ultrasound machines will be more advanced in the coming years and more hospitals will be able to purchase these advanced machines. Consequently, Doppler will be more widely available. As Doppler is more difficult, with a longer learning curve than the widely used grey-scale ultrasound, measurement of endometrial thickness will most probably always be the first step in ultrasound assessment. And because women with postmenopausal bleeding and endometrial thickness ≥ 5mm have a high risk (1 in 4) of endometrial cancer.[1,2,12,13] it is always necessary to obtain an adequate endometrial sample for histological diagnosis in these women. Obtaining histology can be performed by endometrial sampling or hysteroscopy, which we will discuss later. However, sometimes it is not possible to measure the endometrial thickness with grey-scale ultrasound or it is not possible to obtain adequate histology by endometrial sampling. In these situations, Doppler could be used to select women with a high risk of endometrial (pre) cancer for hysteroscopy. Prediction models using Doppler have been published, but none of these have been externally validated yet.[1,12,13] Additionally, Doppler could be used in women with a thickened endometrium to distinguish between women with an endometrial polyp or diffuse thickened endometrium and this could be used to decide for therapeutic hysteroscopy. Therefore, future research should focus on the diagnostic performance of Doppler to diagnose endometrial polyps and on external validation of prediction models using Doppler in women where TVS or endometrial sampling is not possible.

Invasive diagnostic work-up

Further research on the diagnostic work-up of women with PMB should focus on the most cost-effective sequenced combination of tests after performing TVS. As mentioned above, in most guidelines endometrial sampling is currently the next step in the diagnostic work-up after TVS. Endometrial sampling fails in about 40% of women and the sensitivity in women with PMB is much lower than we thought. Because of the risk of endometrial (pre) cancer, these findings warrant hysteroscopy in women with failed endometrial sampling and also in women with benign histology after endometrial sampling to diagnose focal pathology. From this, the question is what strategy is beneficial in what circumstances. Strategies that need to be compared, both from a patient perspective as well as from a cost-effectiveness perspective, are immediate hysteroscopy in all women with PMB and thickened endometrium versus a strategy in which endometrial sampling and SIS and hysteroscopy are combined, in different sequences and different time-paths ('one-stop' versus multiple consultations).

The decision about whether further diagnostic work-up for endometrial polyps and possible focal (pre) cancer is necessary is strongly dependent on the prevalence of endometrial (pre) cancer in the population. Compared to the prevalence known in the literature (5-10% in a population of women with PMB),[14,15] a 6% prevalence in a pre-selected population of women with PMB and a benign result of endometrial sampling seems quite high. Most existing studies on the prevalence endometrial (pre) cancer in a polyp included a combination of pre- and postmenopausal women in mostly small retrospective cohorts of around 100 to 150 women.[16] Because the diagnostic accuracy of a test is strongly dependent on the pre-test probability (prevalence) and the prevalence of endometrial (pre) cancer is much higher in postmenopausal versus premenopausal women, it is important to study large cohorts with postmenopausal women only. We suggest a large prospective cohort study in which all women with PMB and an endometrial thickness of > 4 mm undergo endometrial sampling, SIS and (diagnostic/therapeutic) hysteroscopy. Through this study, we will be able to investigate the prevalence of endometrial (pre) cancer in a polyp in the Netherlands. Furthermore, diagnostic accuracy and costs-effectiveness of different diagnostic pathways could be studied.

If the indication is set for further diagnostic work-up to diagnose focal pathology, one has to decide between direct hysteroscopy or hysteroscopy preceded by SIS. Because more research on the diagnostic accuracy of SIS in postmenopausal women

is needed, it would be interesting to perform a systematic review on the diagnostic accuracy of SIS to diagnose endometrial polyps specifically in women with PMB. The second knowledge gap on the use of SIS is the sequence in which different diagnostic test should be done. It would be most cost-effective and patient-friendly if the SIS would be performed during the first contact with the gynaecologist, together with TVS and endometrial sampling. However, we do not know what the effect is on the accuracy of the tests in case these two are combined. Hypothetically, the fluid could affect the quality of the aspiration, when endometrial sampling is performed after the SIS. Also, performing an endometrial sample first could affect the quality of the ultrasound image of the SIS. One study reported that the proportion of adequate endometrium samples that can be evaluated by the pathologist is higher when endometrial aspiration is done first with subsequent SIS. This study was performed in a mixed population of pre- and postmenopausal women.[17] The optimal sequence of TVS and SIS in combination with endometrium sampling specifically in women with PMB needs to be elucidated. Therefore, we suggest a randomised trial in which patients with PMB are randomly allocated for either SIS and subsequent endometrial aspiration, or in the reverse order. As a primary outcome for this study, we suggest the quality of the endometrial sampling, with the quality of the ultrasound image and pain during the procedures as secondary outcomes.

Prevention and treatment of recurrent bleeding

Because only sparse evidence is available on both prevalence and treatment of recurrent bleeding in postmenopausal women, these aspects should be subject for further research. As we proposed a large cohort study of women with postmenopausal bleeding, we could study the prevalence of recurrent bleeding in this cohort. Furthermore, it would be interesting to study the prevalence of recurrent bleeding in different populations. Regarding the treatment of recurrent bleeding, research should focus on the medical or hormonal treatment of women with PMB where an endometrial carcinoma has been ruled out. To study the effectiveness of hormonal treatment of women with recurrent PMB, we suggest a multi-arm randomised trial:

1. Women with a first episode of postmenopausal bleeding, where endometrial cancer has been ruled out, with a thin endometrium. Randomisation between local vaginal oestrogen therapy and expectant management.

2. Women with a first episode of postmenopausal bleeding, where endometrial cancer has been ruled out, with a thickened endometrium. Randomisation between LNG-IUD placement and expectant management.
3. Women with a first episode of recurrent PMB where endometrial cancer has been ruled out, with a thin endometrium. Randomisation between local vaginal oestrogen therapy and expectant management.
4. Women with a first episode of recurrent PMB where endometrial cancer has been ruled out, with a thickened endometrium. Randomisation between LNG-IUD placement and expectant management.

The primary outcome of this study should be recurrent PMB within one year and secondary outcomes should be endometrial (pre) cancer, cost-effectiveness, side effects and quality of life.

Clinical implications

The results of the research presented in this thesis supports further diagnostic work-up and treatment of endometrial polyps in women with PMB and a thickened endometrium, because of the risk of an underlying endometrial (pre) cancer. The question that remains is concerned with what the most (cost) effective diagnostic pathway is to diagnose and treat these polyps. Hysteroscopy, despite being safe, well tolerated and performed in an outpatient setting, remains an invasive procedure with a potential risk of complications and at considerable cost.[18] Clinicians should therefore be hesitant to routinely incorporate hysteroscopic evaluation in all women with a thickened endometrium. Uterine cavity evaluation (SIS and hysteroscopy) should be performed in a trial setting to gain more knowledge on the prevalence of endometrial (pre) cancer, recurrent PMB and the most (cost) effective diagnostic work-up. On theoretical grounds, SIS should be used to select women with PMB for therapeutic hysteroscopy, after TVS and endometrial sampling.

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Addendum

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List of publications

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P.J. Marang-van de Mheen, **N. van Hanegem**, J. Kievit. Effectiveness of a routine registration to identify adverse outcomes in surgical patients. *Qual Saf Health Care 2005 Oct;14(5):378-82*

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Oral presentations

N. van Hanegem, L. Barroilhet, M.R. Nucci, M. Bernstein, S. Feldman. Fertility-sparing treatment in younger women with adenocarcinoma in situ of the cervix. *Oral presentation at* New England Association of Gyne*cologic Oncologists (NEAGO), June* 2011

N. van Hanegem, M.C. Breijer, M.Y. Bongers, B.W. Mol, A. Timmermans. Diagnostic work-up for postmenopausal bleeding: a randomised clinical trial. *Oral presentation at Global Congress of AAGL in Vancouver, November 2014*

N. van Hanegem. Behandeling van endometriumpoliepen bij postmenopauzaal bloedverlies (The treatment of endometrial polyps). *Invited speaker at Doelencongres in Rotterdam, April 2015*

N. van Hanegem. Pompoen: postmenopauzaal bloedverlies en verdikt endometrium; direct hysteroscopie of ook watercontrastechoscopie? (Postmenopausal bleeding and a thickened endometrium; direct hysteroscopy or preceded by SIS?) *Invited speaker at Doelencongres in Rotterdam, April 2015*

N. van Hanegem. Gynaecologie in London (Gynaecology in London). *Invited speaker at Clustersymposium Maastricht University Medical Centre+, October 4th 2015*

N. van Hanegem. The treatment of endometrial polyps in women with postmenopausal bleeding. *Invited speaker at the Annual Congres of the European Society of Gynaecological Endoscopy (ESGE) in Budapest, October 7th 2015*

Curriculum Vitae

Lennie (Nehalennia) van Hanegem werd geboren op 16 december 1979 in Goes. Na de basisschool en het VWO op SSG Scheldemond te Vlissingen, werd zij uitgeloot voor Geneeskunde en ging zij in 1998 Biomedische Wetenschappen studeren in Leiden. In 1999 werd zij alsnog ingeloot en in 2006 behaalde zij haar artsexamen aan de Universiteit Leiden.

Haar eerste baan als arts was als arts-assistent op de afdeling Obstetrie en Gynaecologie in het Medisch Centrum Alkmaar. Hier heeft zij ook gewerkt gedurende de eerste 1,5 jaar van de opleiding (opleiders Y. van Kasteren en A. Adriaanse), waarna ze deze voortzette in het Academisch Medisch Centrum (opleider M.J. Heineman). Gedurende haar opleiding tot gynaecoloog ging zij voor een wetenschapsstage naar de Verenigde Staten, waar zij onderzoek deed op de afdeling Gynaecologische Oncologie van het Brigham and Women's Hospital (Harvard Medical School) in Boston. Het laatste jaar van haar opleiding bestond uit een differentiatie benigne gynaecologie in het Onze Lieve Vrouwe Gasthuis te Amsterdam (opleider D. Bekedam).

Sinds juni 2013 is Lennie werkzaam als staflid op de afdeling Obstetrie en Gynaecologie van het Maastricht Universitair Medisch Centrum te Maastricht, met als aandachtsgebied minimaal invasieve gynaecologische chirurgie en endometriose. Begin 2015 ging zij voor drie maanden naar Londen voor een fellowship endometriose en minimaal invasieve gynaecologische chirurgie in het Endometriosecentrum van het University College London Hospital.

Lennie woont samen met Martijn Groenleer in Amsterdam en Maastricht en zij verwachten begin 2016 hun eerste kind.

Nehalennia: een Keltisch-Romeinse godin die in het 2e en 3e-eeuwse Gallia Belgica (= het huidige Zeeland) werd vereerd, vooral door zeelui en handelaars. Zij was de godin van de vruchtbaarheid en de beschermvrouwe van reizigers en handelaren in het Noordzeegebied. In de jaren '70 werden verschillende altaren voor Nehalennia gevonden in de Oosterschelde.

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A

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De kliniek

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Privé

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‘Een moordvrouw zijn, is bloedmooi!’

M. Herman, juli 2015