The diagnostic work-up of women with postmenopausal bleeding
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Citation for published version (APA):
van Hanegem, N. (2015). The diagnostic work-up of women with postmenopausal bleeding

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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. Worldwide, people are getting older and the incidence of overweight and obesity is rising. 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.

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.

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. Endometrial polyps are believed to be responsible for recurrent PMB, 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.

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?
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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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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
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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. 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.

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. 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.
General introduction

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

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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. 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. 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%. 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. 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.
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• **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.
References

Chapter 1


