Management of endometrial abnormalities in postmenopausal women, an individualized approach
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Summary and General discussion
**SUMMARY**

The goal of this thesis is to evaluate different diagnostic strategies for women with postmenopausal bleeding (PMB), including strategies based on individual probabilities and to study the value of endometrial thickness measurement in asymptomatic postmenopausal women.

**Chapter 2** presents a systematic review on existing prediction models for endometrial cancer in women with PMB. We identified nine studies reporting on the development and validation of prediction models in women with PMB. From the data we identified the most important predictor variables, which could be roughly divided into four subjects: patient characteristics, gray-scale transvaginal sonography (TVS) variables, Doppler TVS variables and hysteroscopy variables. Most prediction models used a combination of these subjects to predict the chance of endometrial cancer. Eight of these studies described at least one aspect of internal validation and none of the prediction models was externally validated. Models including power Doppler showed the best performance in internal validation, but based on the difficult use of Doppler in general gynecological practice, we concluded that the best models up to present are prediction models combining patient characteristics with endometrial thickness.

In **Chapter 3** we evaluated the cost-effectiveness of strategies incorporating the diagnostic value of patient characteristics for endometrial carcinoma using prediction models with a decision analytic approach. We designed a decision analytic model to compare four diagnostic strategies for women with PMB. (1) The ‘patient characteristics’ strategy, i.e. probability estimates based on characteristics of the women and histological analysis in case the probability of (pre)malignancy exceeded 4%. In this strategy, TVS is not performed. (2) The ‘sequential’ strategy, i.e. probability estimates based on characteristics of the women, with TVS in case the probability for cancer exceeded 4% and subsequent histological analysis when the endometrial thickness exceeds 4mm. (3) The ‘integrated’ strategy, i.e. TVS in all women, with a probability estimate based on both characteristics of the women and TVS results, completed by histological analysis when the probability of cancer exceeded 4%. The three model based strategies were compared to a strategy with endometrial thickness measurement reflecting current practice. Strategy (1), selecting women for endometrial biopsy based on their history only, dominated all other strategies (more effective, less costs). In a clinical scenario where TVS was assumed to be an integral part of the consultation without additional costs, a strategy selecting high-risk women for TVS (the ‘sequential’ strategy) became the most cost-effective strategy.
For a successful implementation, a prediction model should be validated externally in an independent population. Chapter 4 describes the external validation of two previously developed models predicting endometrial cancer in women with PMB: the ‘patient characteristics’ model and the ‘patient characteristics and TVS’ model. We applied the models on two independent databases collected in the Netherlands and Sweden to assess the diagnostic performance of the models. In both the Dutch and the Swedish databases discrimination for the ‘patient characteristics and TVS’ model showed an AUC of 0.89 (95% CI 0.86-0.91/92), which was higher compared to the AUC for the ‘patient characteristics’-model, 0.71 (95% CI 0.65-0.76) and 0.69 (95% CI 0.64-0.73) respectively. The calculated AUC for TVS-only was 0.87 in the Dutch Database (95% CI 0.83-0.90) and 0.90 in the Swedish database (95% CI 0.88-0.93). This study shows that after external validation in two independent datasets, the existing multivariable models maintain their diagnostic performance and are able to distinguish between women with low or high risk of endometrial cancer in women with PMB. The ‘patient characteristic and TVS’ model however, offers no diagnostic advantage over the measurement of endometrial thickness alone. 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.

In a substantial number of cases, endometrial sampling fails because of technical problems or because of an insufficient amount of tissue for a histological diagnosis. In Chapter 5 we investigated which doctor and patient related factors contribute to failure of outpatient endometrial sampling in women with PMB and an endometrial thickness > 4 mm. Nulliparity and advanced age were associated with failure and an endometrial thickness > 12 mm decreased the chance of failure. Training level was not associated with technical failure or insufficient sampling. A prediction model for total failure was subsequently designed. The AUC of the model was 0.64 (95% CI 0.58-0.70) indicating a moderate capacity to discriminate between women with a high or a low risk of failure.

Chapter 6 evaluates the use of the prediction model for a failed endometrial biopsy to reduce costs for the same accuracy of diagnostic testing in women with PMB through a cost-minimization analysis. If the probability of failure exceeds 65% it is less costly to refer the patient immediately for outpatient hysteroscopy with biopsy, instead of an attempt for outpatient endometrial biopsy. However this is only a cost-reduction of three euro’s per patient, so we concluded that individualizing the decision to perform endometrial biopsy or hysteroscopy in women presenting with PMB based on patient characteristics is unlikely to increase the efficiency of the diagnostic work up.
No guidelines on standardized assessment of endometrial biopsy specimens are available, which results in a diagnosis that is influenced by subjectivity, with a high inter-pathologist variability. The objective of Chapter 7 was to determine whether structured assessment of outpatient endometrial biopsy specimens with strict criteria decreases the amount of inconclusive samples due to insufficient material. We requested 66 and retrieved 36 endometrial samples from eight different hospitals that were collected during the normal diagnostic work-up and assessed as insufficient for reliable histological diagnosis. Structured reassessment of the retrieved samples by one pathologist specialized in gynecology did not change the conclusion in 35 of the 36 samples. Only one sample contained a large amount of endometrial tissue and the final diagnosis was endometrial hyperplasia without atypia. All other samples contained insufficient material for a reliable diagnosis.

Our findings suggest that although it might be helpful for pathologists to have diagnostic criteria for adequacy and/or inadequacy of an endometrial biopsy sample, the gain in efficiency is likely to be small. We therefore think that to increase the effectiveness of outpatient endometrial biopsies, effort has to be made to obtain as much material as possible to minimize the failure of endometrial biopsies due to insufficient material.

Measurement of endometrial thickness is an important tool in the assessment of women with PMB. The relevance of endometrial thickness measurement by ultrasound in asymptomatic women is unclear. Chapter 8 describes a systematic review and meta-analysis to address: (I) the normal endometrial thickness measured by TVS, (II) the prevalence of endometrial pathology and (III) the sensitivity and specificity of endometrial thickness measurement by TVS for diagnosing (pre-) malignant endometrial disease in asymptomatic postmenopausal women. We included 32 studies reporting on 11,100 women to answer our three objectives: (I) The estimated mean endometrial thickness was 2.9 mm (95% CI 2.6-3.3). (II) The pooled estimated prevalence of endometrial carcinoma and atypical endometrial hyperplasia were 0.62% (95% CI 0.42-0.82), and 0.59% (95% CI 0.22-0.96), respectively. (III) Summary estimates for sensitivity and specificity of TVS endometrial thickness measurement were 0.83 (95% CI 0.19-1.00) and 0.72 (95% CI 0.32-0.93) for 5 mm cut-off and 0.33 (95% CI 0.04-0.85) and 0.94 (95% CI 0.92-0.96) for 6 mm cut-off. The results from this systematic review do not justify the use of endometrial thickness as a screening test for endometrial carcinoma and atypical endometrial hyperplasia in asymptomatic postmenopausal women not using HRT.
GENERAL DISCUSSION

The studies presented in this thesis focus on an individualized approach for women with PMB. We assessed the cost-effectiveness of an individualized approach and externally validated a prediction model for endometrial cancer in women with PMB. Furthermore, we studied the value of endometrial thickness measurement in asymptomatic postmenopausal women. Below, we discuss the implications of the main findings in this thesis for clinical practice and future research.

Cost-effectiveness and external validation of prediction models for endometrial cancer in women with postmenopausal bleeding.

In the current diagnostic work-up for PMB, an endometrial thickness cut-off value of 4 mm is used to determine whether a patient needs further invasive testing for endometrial carcinoma. This cut-off value of 4 mm advised by Dutch guidelines is based on a meta-analysis performed by Smith-Bindman et al.\(^1\) The determination of the cut-off value for the Netherlands was based on a 10% pre-test probability, the risk for all women with PMB regardless of other risk factors.\(^2\) While the probability of PMB decreases with increasing age,\(^3\) the probability of endometrial cancer increases significantly with increasing age.\(^4\) Depending on other risk factors including age, time since menopause, obesity, hypertension, diabetes mellitus and reproductive factors, the risk of endometrial cancer varies between 1% and 24%.\(^3,5-10\) However, in currently used guidelines individual patient characteristics are not taken into account. Previous systematic reviews showed that TVS and hysteroscopy both have high individual accuracy in predicting endometrial (pre) malignancy.\(^11,12\) In these studies the diagnostic tests are evaluated for accuracy against a reference standard, independent of their clinical context or individual patient characteristics. Estimates of diagnostic accuracy derived in this way ignore information that may have been acquired earlier in the diagnostic process. Such an approach can lead to erroneous inferences and may artificially increase the value of diagnostic tests.\(^13\) Inclusion of individual patient characteristics could result in a more individualized and possibly more accurate and efficient work up strategy. In this strategy, a very high a priori chance of endometrial carcinoma warrants further histological testing, whereas women with a very low prior chance might be reassured even without TVS.

Our group developed two multivariate models to calculate the individual risk of endometrial carcinoma in women with PMB, which showed good accuracy in internal validation.\(^14\) In this thesis, these previously developed ‘patient characteristics’ and ‘patient characteristics and TVS’ models,\(^14\) were externally validated in two independent databases. Both models maintained their diagnostic performance in two independent databases. We compared the ‘patient characteristics and TVS’ model with endometrial thickness measurement alone. This led to new insights on the applicability of the model. The study presented in Chapter 3 showed that the ‘patient characteristics and TVS’ model is slightly more cost-effective...
than TVS alone but the diagnostic performance is comparable. We believe that in clinical practice, due to the complexity of the prediction model, TVS alone outweighs this small increase in cost-effectiveness. The ‘patient characteristics’ model, to be used without an ultrasound, has a much lower diagnostic accuracy than TVS alone. Nevertheless, this ‘patient characteristics’ model could be used to reassure women without further (invasive) testing in situations where an ultrasound is not immediately available in the physicians’ office, for example in primary care or in a health system where additional TVS has to be ordered separately and be performed by a radiologist. In clinical practice, a woman can be reassured without TVS and without further testing if she is aged 50 years or younger and has up to one additional risk factor.

**Efficiency of minimally invasive endometrial biopsy.**

In case of an endometrial thickness of more than 4 mm, further histological assessment with an endometrial sampling device is advised: the Dutch guideline advises a Pipelle® endometrial sampling device.\(^2\) The Pipelle® endometrial sampling device has the highest sensitivity in postmenopausal women (99.6%), compared to other sampling devices.\(^{15}\) A major drawback of this technique is the high failure rate due to technical problems (12-23%) or because of an insufficient amount of material for a reliable diagnosis (16-68%).\(^{16-19}\) We hypothesized that less experienced professionals would have a higher endometrial biopsy failure rate. The multivariable analysis presented in Chapter 5 showed that only patient characteristics contributed to the failure of outpatient endometrial biopsies and thus, inexperience was not a risk factor for failure. With a moderate accuracy, a prediction model based on patient characteristics can predict the failure of an endometrial biopsy. Individualizing the decision to perform an endometrial biopsy of hysteroscopy in women presenting with PMB based on patient characteristics is unlikely to increase the efficiency of the diagnostic work up. In our study, the failure rate of endometrial biopsies due to insufficient material was 30%. At subsequent testing, we found a (pre-) malignancy in 7% of these women. In a study performed by Van Doorn et al. an endometrial (pre-) malignancy was diagnosed in 6% of the women with an insufficient sample.\(^{18}\) Therefore, women with postmenopausal bleeding and a failed endometrial biopsy cannot be reassured without further testing. Pathologists feel that it would be useful if criteria for adequacy and/or inadequacy of an endometrial biopsy were proposed.\(^{20}\) We evaluated such criteria by applying them on samples that were assessed as insufficient in Chapter 7. This did not change the conclusion in all but one of the samples. Therefore, we concluded that the gain in efficiency of such criteria is likely to be small. In order to increase the effectiveness of outpatient endometrial biopsies, effort has to be made to obtain as much material as possible to minimize the failure of endometrial biopsies due to insufficient diagnosis. Further research should focus on the best way to achieve this improvement.
Asymptomatic postmenopausal women

Also women not suffering from PMB sometimes undergo TVS, when visiting the gynecologist for other indications such as prolapse or abdominal complaints. Inevitably, the endometrium is visualized by TVS and a thickened endometrium may then be observed. The prevalence of endometrial cancer and endometrial hyperplasia in postmenopausal women without bleeding symptoms and without HRT is very low. Endometrial thickness measurement in this population cannot achieve a sufficiently high sensitivity to provide additional reassurance to women with a negative test nor achieve a sufficiently high specificity to justify further invasive testing in women with a positive test. Therefore, endometrial thickness measurement has no value in women without PMB. The clinician should decide on an individual patient basis for further diagnostic evaluation.

Current diagnostic work-up

When a woman presents with PMB at a general practitioner, he or she will refer her to a gynecologist to exclude the presence of endometrial carcinoma. Current guidelines are not clear and unambiguous about the diagnostic pathway. Based on the available evidence, we think that measurement of endometrial thickness should be the first step in the diagnostic pathway. If endometrial thickness is more than 4 mm, further invasive testing, by endometrial biopsy, is warranted. Pathology results can be: 1. (pre) malignancy; 2. benign; or 3. insufficient. If endometrial biopsy shows an insufficient sample, we confirmed in Chapter 7 that further testing by hysteroscopy is indicated because of an increased risk of endometrial carcinoma. If endometrial biopsy shows a benign result, the Dutch guideline is not clear about further diagnostic work up. The individual doctor can decide for expectant management or further invasive testing by hysteroscopy. To answer this clinical question, we designed the POMPOEN trial (effectiveness of saline-infused sonography and hysteroscopy in the work-up of women with PMB), which is currently still including patients. In this trial, women with PMB, an endometrial thickness > 4 mm and a benign endometrial biopsy are randomized to either expectant management or uterine cavity assessment (and if necessary treatment) with saline infused sonography (SIS) and hysteroscopy. Primary outcome of this study is recurrence of PMB after twelve months. If hysteroscopy for benign pathology is proven to be effective, we need to reconsider the added value of office endometrial biopsy in the work-up for women with PMB. Until the POMPOEN trial is finished, we would like to propose a diagnostic work-up presented in Figure 1.
Figure 1.

Future research

The POMPOEN trial will answer the question whether or not treatment of benign endometrial pathology is effective in women with an endometrial thickness > 4 mm. The diagnostic flow chart shown in Figure 1, should be updated according to the results of this trial, and implemented in guidelines on women with PMB. Before changing current guidelines, it is important to know the implementation in clinical practice of the guideline at this moment.
The Dutch guideline only recommends further testing when SIS or office-hysteroscopy is possible. However, most resections of endometrial polyps are still performed under general anesthesia.\(^{21}\) By studying the variety in clinical practice of TVS, endometrial biopsy, SIS and hysteroscopy throughout our country insight is obtained in the implementation of current guidelines. Furthermore, the impact of reassurance of women with a low risk of cancer without further research needs to be evaluated after implementation in clinical practice.
REFERENCES


