Management of endometrial abnormalities in postmenopausal women, an individualized approach
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Citation for published version (APA):

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Comparing two diagnostic strategies based on the predicted probability of a failed endometrial biopsy in women with postmenopausal bleeding: a cost-minimization analysis

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ABSTRACT

Objective: To evaluate whether a model to predict a failed endometrial biopsy in women with postmenopausal bleeding and an endometrial thickness > 4.0 mm can reduce costs for the same accuracy through a cost-minimization analysis.

Study design: A decision analytic model was designed to compare two diagnostic strategies for women with postmenopausal bleeding: (I) Attempt office endometrial biopsy and perform outpatient hysteroscopy after failed biopsy and (II) Endometrial biopsy or direct referral to outpatient hysteroscopy based on the predicted probability of a failed endometrial biopsy. Robustness of assumptions regarding costs was evaluated in sensitivity analyses.

Results: At different cut-offs for the predicted probability of failure of an endometrial biopsy, strategy (I) was generally less expensive than strategy (II). The costs for strategy (I) were always € 460; the costs for strategy (II) varied between € 457 and € 475. At a 65% cut-off, a possible saving of € 3 per woman could be achieved.

Conclusions: Individualizing the decision to perform an endometrial biopsy or hysteroscopy in women presenting with postmenopausal bleeding based on patient characteristics is unlikely to increase the efficiency of the diagnostic work up.
INTRODUCTION

Postmenopausal bleeding (PMB) is the most common presenting symptom of endometrial cancer and warrants further investigation. Since the 1990s endometrial thickness measured by transvaginal ultrasound was introduced to select women for further invasive diagnostic testing to detect or rule out endometrial cancer. Although the optimal endometrial thickness cut-off for women with PMB still remains questionable, at present most guidelines advise an endometrial thickness cut-off of 4 mm or 5 mm to select patients for further histological verification. Outpatient endometrial biopsy is the least invasive technique to obtain material for histological assessment. Pipelle® endometrial biopsy (Pipelle de Cornier, Paris, France) is the most accurate endometrial sampling device to detect endometrial carcinoma and endometrial hyperplasia in patients with PMB. Furthermore, a strategy with endometrial biopsy after endometrial thickness measurement is the most cost-effective diagnostic strategy for patients with PMB.

Although endometrial biopsy is the most accurate and frequently used diagnostic procedure it has some major drawbacks in clinical practice. In 12-21% of cases, endometrial sampling fails due to technical reasons and in 7-68% of cases the amount of tissue obtained is insufficient for a reliable histological diagnosis. Because an endometrial (pre-) malignancy is present in 6-23% of the women with a failed endometrial biopsy, these patients cannot be reassured without further more invasive investigations.

In a previous publication we described a multivariable prediction model to predict the probability of a failed endometrial biopsy in women with PMB. The purpose of the current study was to evaluate whether this model has the potential to reduce costs for the same accuracy of diagnostic testing in women with PMB through a cost-minimization analysis.

METHODS

We performed a cost-minimization analysis using a decision analytic approach. The aim was to evaluate whether individualizing the decision to perform a diagnostic hysteroscopy rather than an endometrial biopsy in women with a first episode of PMB can decrease the costs of the diagnostic work-up. This decision can be based on the probability of a failed biopsy, estimated with a clinical prediction model based on patient characteristics. In a previous publication, we described the development of a model to predict the risk of a failed endometrial biopsy in women presenting with PMB and an endometrial thickness of more than 4.0 mm. Details on model development are presented in the original paper. In short, data on 356 women with PMB were included in a multivariable regression analysis. Characteristics satisfying the criteria for inclusion in the model were time since menopause, hypertension, endometrial thickness (categorized) and nulliparity. Endometrial biopsy failed in 44.4% (95% CI: 39.3-49.6%) of the women (158/356). The discriminative capacity
of the model was assessed with the area under the receiver operator characteristic curve and was 0.66 (95% CI 0.60–0.72). The calibration of the model was good e.g. there was high agreement between the predicted probabilities and the observed proportion of failed endometrial biopsies.

**Cost minimization analysis**

The cost minimization analysis compared two diagnostic strategies: (I) Attempt office endometrial biopsy in all women and perform outpatient hysteroscopy after failed biopsy and (II) Decision for endometrial biopsy or direct referral to outpatient hysteroscopy based on the model based probability of a failed biopsy. The diagnostic strategies are represented in Figure 1. The sensitivity and specificity associated with different failure rate cut-offs were calculated in the prospective cohort. As the individualized strategy may become cost saving at a certain cut-off, an analysis was performed to identify this cut-off.

![Figure 1. Flowchart representing the two diagnostic strategies.](image-url)
Assumptions
Outpatient hysteroscopy with biopsy was assumed to be the gold standard and had a 100% success rate. Furthermore we assumed that in all women diagnostic investigations are continued until adequate material for a histological diagnosis is obtained thus, all women in whom endometrial biopsy failed are subsequently referred to outpatient hysteroscopy with biopsy. With both strategies material for diagnosis will be obtained in all patients.

Costs
The analysis was conducted from a health care provider’s perspective and included direct medical costs in euro’s (Table 1). Costs were estimated using Dutch reference unit costs and local cost calculations (Academic Medical Center Amsterdam). Costs for outpatient hysteroscopy were estimated costs per procedure and included costs for maintenance, disinfection and sterilization. Costs for an outpatient clinic visit included the specialist fee, costs for the assisting personnel and overhead costs.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cost (€)</th>
<th>Range (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient appointment (first visit)</td>
<td>129</td>
<td>60-250</td>
</tr>
<tr>
<td>Outpatient appointment (follow up visit)</td>
<td>65</td>
<td>30-135</td>
</tr>
<tr>
<td>Outpatient appointment (hysteroscopy clinic visit)</td>
<td>194</td>
<td>100-400</td>
</tr>
<tr>
<td>Hysteroscopy including endometrial biopsy and pathologists fee, maintenance and sterilization</td>
<td>144</td>
<td>70-250</td>
</tr>
<tr>
<td>Endometrial biopsy during outpatient visit including pathologists fee</td>
<td>89</td>
<td>40-150</td>
</tr>
</tbody>
</table>

Statistical analyses
Analyses were performed using TreeAgePro 2008 (TreeAge Software Inc, Williamstown, Mass). In addition to the base-case analysis, evaluating the results for the most likely estimates of model parameters, one-way sensitivity analyses were carried out to explore the robustness of the results for uncertainty in these parameters, including model accuracy, incidence of failure, and cost estimates.

RESULTS
In this economic analysis, expected costs for the two diagnostic strategies were compared. As endometrial biopsy failed in 44% of the patients in the cohort study, this percentage was used for strategy I. In the prospective cohort, the predicted probability of failure varied between 22 and 73%. The sensitivity and specificity of a 50, 55, 60, 65 and 70% predicted failure cut-off is reported in Table 2. In the base-case analysis, expected costs for the two
strategies were comparable. Only at a 65% predicted failure cut-off, strategy II appeared to be less costly than strategy I. At this threshold, strategy II would result in a saving of € 3 per patient presenting with PMB (Table 2).

Table 2. Accuracy, uncertainty and impact of cut-off values for predicted probability of a failed endometrial biopsy in women with postmenopausal bleeding and endometrial thickness > 4.0 mm

<table>
<thead>
<tr>
<th>Cut-off failure probability (%)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Costs Strategy I (€)</th>
<th>Costs Strategy II (€)</th>
<th>Expected difference (strategy II – strategy I) (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>0.30 (0.25 – 0.35)</td>
<td>0.86 (0.81 – 0.91)</td>
<td>460</td>
<td>472</td>
<td>12</td>
</tr>
<tr>
<td>55</td>
<td>0.21 (0.16 – 0.26)</td>
<td>0.92 (0.87 – 0.97)</td>
<td>460</td>
<td>475</td>
<td>15</td>
</tr>
<tr>
<td>60</td>
<td>0.14 (0.09 – 0.19)</td>
<td>0.96 (0.91 – 1.0)</td>
<td>460</td>
<td>460</td>
<td>0</td>
</tr>
<tr>
<td>65</td>
<td>0.075 (0.025 – 0.125)</td>
<td>0.99 (0.94 – 1.0)</td>
<td>460</td>
<td>457</td>
<td>-3</td>
</tr>
<tr>
<td>70</td>
<td>0.008 (0.0 – 0.06)</td>
<td>0.99 (0.94 – 1.0)</td>
<td>460</td>
<td>462</td>
<td>2</td>
</tr>
</tbody>
</table>

All sensitivity analyses performed for cost variables to explore robustness of the results for uncertainties in cost-estimates, showed results consistent with the base case analysis. For a cut-off value of 65%, the minimal expected cost-difference between strategy I and strategy II was € 1 and the maximal expected cost-difference was € 5 (Table 3). A sensitivity analysis varying the percentage of failure showed that strategy I is always cost-effective if the failure rate of endometrial biopsies is 25% or less.

Table 3. Sensitivity analysis: minimum and maximum expected costs and cost-difference for 65% cut off value.
DISCUSSION

In this study we performed a cost-minimization analysis to investigate the potential for cost savings of selecting women with a first episode of PMB for endometrial biopsy or hysteroscopy based on the predicted probability of a failed biopsy. At a cut-off of 65% predicted failure rate, there is possibly a very small saving per patient presenting with PMB. The strength of this analysis is the new approach to the problem of a failed endometrial biopsy in women with PMB. Increasingly, clinical prediction models are developed for clinical practice. Before a model can be implemented in clinical practice, the external validity and impact on cost-effectiveness has to be evaluated.

A limitation of our study is the model based approach. As for all model based studies, the validity of the model depends on the model input parameters and assumptions. We assumed that a hysteroscopy, as golden standard diagnostic procedure, would always succeed and lead to a diagnosis. We also assumed that an outpatient endometrial biopsy if successful, would lead to a reliable diagnosis. Another possible limitation is the costs used in our analyses. Because precise economic data are not available, we used the best available data that could be acquired from national and local sources. The work-up in the model was conform recommendations in the national guideline on the work-up for women with PMB. Clark and colleagues investigated the cost-effectiveness of initial diagnostic strategies for women with PMB. Their conclusion was that depending on the prevalence of endometrial malignancy, an endometrial biopsy after endometrial thickness measurement with a cut-off 4 or 5 mm was the most cost-effective strategy. In this analysis however, the probability of a failed endometrial biopsy was 12% and in contrast to our current study, this probability was independent of patient characteristics.

Because the implementation of a prediction model in clinical practice is time consuming, the model should be easy applicable and the benefits in terms of cost-effectiveness should be substantial. In view of the results of our study, the potential value of using the prediction model for a failed endometrial biopsy in women presenting with PMB appears to be limited and not contributing to a more efficient use of health care resources. Based on the current study, we recommend outpatient endometrial biopsy for all women presenting with a first episode of PMB and an endometrial thickness more than 4.0 mm. Patients in whom endometrial biopsy fails have 6-23% risk of an endometrial (pre-)malignancy and cannot be reassured without further testing. In case of a failed endometrial biopsy, a hysteroscopy with guided biopsy should be performed. Future research should, to increase the efficiency of the diagnostic work-up for women with PMB, focus on decreasing the amount of failed endometrial biopsies.
REFERENCES


