The diagnostic work-up of women with postmenopausal bleeding
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Chapter 6

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


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.
Chapter 6

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.\textsuperscript{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.\textsuperscript{16}

Participants

Women could be included if they had PMB, an endometrial thickness of $> 4 \text{ mm}$ 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. 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. 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.
Chapter 6

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

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

DHA = Dutch Healthcare Authority, MUMC = Maastricht University Medical Centre, NHI = National Healthcare Institute
Figure 1. Study flowchart

200 women with PMB

Expectant management

- Recurrent bleeding +
  - n=18
  - Expectant management

- Recurrent bleeding -
  - n=82
  - Expectant management

Diagnostic

- n=34
- n=2 lost to follow-up

Therapeutic

- n=53
- n=2 lost to follow-up

Hysteroscopy

- n=98
- n=87 hysteroscopy
- n=11 expectant

Therapeutic

- n=53
- n=3 no polyp, biopsy
- n=5 polyp, biopsy
- n=45 polyp, polypectomy
  (n=6 inpatient)

Hysterectomy + BSO

- n=7
- No (pre)cancer

No (pre)cancer

- n=92

Recurrent bleeding +
- n=18
- Expectant management

Recurrent bleeding -
- n=82

TVS + sampling

- n=4

(Pre) cancer
- n=6

(Pre) cancer
- n=1

Recurrent bleeding -
- n=82
- Expectant management

Diagnostic

- n=34
- n=2 lost to follow-up

Therapeutic

- n=53
- n=2 lost to follow-up

Hysteroscopy

- n=98
- n=87 hysteroscopy
- n=11 expectant

Therapeutic

- n=53
- n=3 no polyp, biopsy
- n=5 polyp, biopsy
- n=45 polyp, polypectomy
  (n=6 inpatient)

Hysterectomy + BSO

- n=7
- No (pre)cancer

No (pre)cancer
- n=92
Chapter 6

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%).\textsuperscript{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

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

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Scenario</th>
<th>ΔE (95% CI)</th>
<th>ΔC (95% CI)</th>
<th>ICER</th>
<th>CE plane</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NE</td>
<td>SE</td>
</tr>
<tr>
<td>Recurrent blood loss</td>
<td>Without SIS</td>
<td>-0.03 (-0.13 ; 0.08)</td>
<td>780 (550 ; 1158)</td>
<td>28865</td>
<td>69%</td>
</tr>
<tr>
<td>Detection of carcinoma</td>
<td>Without SIS</td>
<td>0.07 (0.03 ; 0.14)</td>
<td>780 (550 ; 1158)</td>
<td>10917</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>With SIS*</td>
<td>0.07 (0.03 ; 0.14)</td>
<td>634 (408 ; 996)</td>
<td>8913</td>
<td>100%</td>
</tr>
</tbody>
</table>

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)
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.
Cost-effectiveness

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. 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. 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. Another explanation could be that the prevalence of endometrial (pre) cancers is different in different populations.

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. 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.

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.

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.

**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. 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 € 19,500 /detected (pre) cancer and for hysteroscopy preceded by a SIS € 16,000 /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.
Chapter 6

References

Cost-effectiveness


