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### Postmenopausal bleeding : studies on the diagnostic work-up

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# 1

## General introduction

Abnormal postmenopausal bleeding (PMB) can be defined as uterine bleeding occurring at least one year after menopause. PMB is a common clinical problem in both general and hospital settings.<sup>1,2</sup> The incidence of spontaneously occurring PMB in the general population can be as high as 10% immediately after menopause.<sup>3</sup> Moreover, in 10-15% of the women with PMB endometrial carcinoma is diagnosed.<sup>4,5</sup>

Endometrial cancer presents itself with PMB in more than 95% of women.<sup>6</sup> The incidence of PMB decreases with age, while the incidence of endometrial carcinoma increases.<sup>7</sup> Furthermore, the probability of endometrial carcinoma in women with PMB rises from less than 1% in women younger than 50 years to 23.8% in women older than 80 years.<sup>7</sup>

Although patients with PMB have an increased risk for endometrial carcinoma, the majority of the patients will have non-malignant endometrium, atrophy or benign pathology. A frequent finding in women with PMB are benign endometrial polyps, with a prevalence ranging between 20 to 40%.<sup>4,5,8</sup>

It is due to this risk of endometrial carcinoma that diagnostic assessment of women with PMB focuses on the exclusion of (pre)malignant disease. Since two decades transvaginal ultrasonography (TVU) has become in use widely to evaluate the endometrium in women with PMB. Prior to the introduction of TVU, women with PMB were scheduled for dilatation and curettage (D&C). The goal of TVU assessment of the endometrium is to exclude endometrial pathology.

Different guidelines in various countries advise measurement of endometrial thickness by TVU as a first step in the evaluation of women with PMB.<sup>9-13</sup> These guidelines are based on various studies summarized in the meta-analysis by Smith-Bindman *et al.*<sup>14</sup> The meta-analysis by Smith-Bindman *et al.*<sup>14</sup> was the first one published on this subject. Several years after that two other meta-analyses were published.<sup>15,16</sup> Although three meta-analyses<sup>14-16</sup> on this subject were published, guidelines have mostly implemented the meta-analysis of Smith-Bindman *et al.*<sup>14</sup> Furthermore, the meta-analysis by Smith-Bindman *et al.*<sup>14</sup> is the most cited publication (total citation 169 by Web of Science) compared to the other two meta-analyses (both total citation 37).<sup>15,16</sup>

The meta-analysis of Smith-Bindman *et al.*<sup>14</sup> used traditional methods of combining published data from different studies. Using the reported data, 2x2 tables per included study were constructed that compared endometrial thickness measured at TVU to presence or absence of endometrial carcinoma. Results across studies were combined in a summary Receiver Operator Characteristics (ROC) Curve. At a 5 mm cut-off the sensitivity for detecting endometrial cancer was 96% for a 39% false-positive rate. Such a combination of sensitivity and specificity

would reduce a pre-test probability of 10% for endometrial cancer to a post-test probability of 1%. Based on this post-test probability, expectant management is at present recommended to these women. In contrast, the two other lesser quoted meta-analyses came to different conclusions.<sup>15,16</sup>

Gupta *et al.*<sup>15</sup> conducted a comprehensive systematic review in which they focused on the study quality assessment of each study. Only four studies were identified as best-quality studies.<sup>17-20</sup> For each article a 2x2 table was constructed and likelihood ratios (LR) were calculated. Pooling of the results of these four studies for endometrial thickness  $\leq 5$  mm resulted in a LR of a negative test of 0.16. Such a LR would implicate that in a patient with a negative test result a pre-test probability of 10% would change to a post-test probability of 2.5%.

Tabor *et al.*<sup>16</sup> included only studies from which they were able to get the original data from the authors. For each study they calculated median endometrial thickness per center and used multiples of the median for endometrial thickness to pool data. They reported a sensitivity of 96% for a specificity of 50% and concluded that such a sensitivity with a 4% false-negative rate was too high. Therefore, in their opinion endometrial thickness measurement does not reduce the need for invasive diagnostic testing.

Based on the meta-analysis by Smith-Bindman *et al.*<sup>14</sup> the Dutch guideline on PMB advocates expectant management once malignancy has been excluded by TVU (i.e. endometrial thickness  $\leq 4$  mm).<sup>9</sup> Adherence to this guideline has been shown to be fairly good: 2/3 of women presenting with PMB are managed conform this guideline.<sup>21</sup> This adherence study demonstrates that in the Netherlands expectant management in women with PMB after exclusion of malignancy by TVU is at present generally accepted.<sup>21</sup>

Although guidelines leave room for individual choices, the preference of the patients has never been systematically taken into account when these guidelines were made. The question is to what extent women are willing to accept a higher probability of cancer ( $> 1\%$ ) associated with expectant management in case of thin endometrium, in order to avoid further invasive procedures. Although current guidelines presume that women consider this small risk as acceptable, empirical data on this presumption are lacking.

The usefulness of endometrial thickness measurement in women with PMB might thus be overestimated. Not only is the preference of the patient unclear, but it is also questionable what the diagnostic accuracy of endometrial thickness measurement is.

Although the diagnostic assessment of women with PMB focuses on exclusion of (pre)malignant disease, further diagnostic assessment may centre on benign intrauterine pathology

(i.e. endometrial polyps). This diagnostic assessment can be undertaken at the first episode of PMB, after exclusion of malignancy or after expectant management in case the bleeding persists or recurs.<sup>9-11</sup> Since endometrial polyps in women with PMB have a prevalence ranging between 20% and 40%, diagnostic assessment of benign disease aims to detect this pathology. Saline Infusion Sonography (SIS) as well as hysteroscopy are highly accurate in diagnosing focal endometrial pathology with comparable diagnostic accuracy with SIS.<sup>22,23</sup> Hysteroscopy has the advantage of allowing simultaneous removal of intracavitary pathology at the time of diagnosis. The Dutch guideline on PMB first became available in 1997.<sup>9,24</sup> The revised version differed from the first version only with respect to the recommendation of performing a SIS or an office hysteroscopy in women with endometrial thickness > 4 mm.<sup>9</sup> In hospitals without access to these ambulatory procedures further uterine cavity evaluation is not advised.

Traditionally hysteroscopy was performed under general anaesthesia. With the development of smaller diameter hysteroscopic systems and the introduction of a “vaginoscopic” approach to hysteroscopy, patient compliance has improved considerably and hysteroscopy nowadays can be performed in an outpatient setting without the use of anaesthesia.<sup>25</sup> New developments in hysteroscopic armentarium and the smaller diameter hysteroscopic systems (3.5-5.5 mm diameter) have made outpatient hysteroscopic surgery possible.<sup>26</sup> Large series of outpatient hysteroscopic polypectomy have been described.<sup>26,27</sup> Furthermore outpatient hysteroscopic polyp removal has been reported to be better than its traditional inpatient counterpart with respect to cost-effectiveness, and patient’s satisfaction rates.<sup>28-31</sup> In contrast, outpatient hysteroscopic polyp removal does not seem to be widely available.<sup>30</sup>

The recommendation to perform SIS or office hysteroscopy to detect benign intrauterine pathology implicitly suggests that treatment of such pathology will be beneficiary to the patient. A benefit could be that patients experience less recurrent PMB if benign intrauterine pathology is diagnosed and treated at first work-up. Another possible benefit could be that hysteroscopy detects more patients with malignancy than office endometrial sampling. At present, hysteroscopy or SIS can be incorporated in the diagnostic work-up at first episode of bleeding or in case the bleeding persists or recurs.<sup>9-11</sup> Few studies report on the incidence of recurrent PMB, with incidences varying between 6% to 40%.<sup>12,32-35</sup> None of these studies related initial diagnostic work-up to the incidence of recurrent PMB. This issue raises several questions. First, it can be questioned what the recurrence rate of bleeding after a first episode of PMB is. If the recurrence rate would be low, then a policy with TVU and office endometrial sampling would be sufficient. Second, it is questionable if the recurrence rate of PMB depends on the performance and outcome of the initial diagnostic work-up, i.e. whether women with a hysteroscopy at the initial work-up experience less recurrent bleeding than patients without hysteroscopy. Third, is malignancy present in women with recurrent bleeding? If, the recurrence rate would be high, or if malignancy would be diagnosed at follow-up, one could advocate that hyster-

oscopy should be applied immediately. Furthermore, if it would be possible to identify those patients at increased risk of recurrent bleeding, one could apply a policy based on individual patient characteristics.

One should keep in mind how diagnostic tests affect patient outcome. Diagnostic hysteroscopy itself does not influence patient outcome. A woman suffering from PMB, in whom hysteroscopy does not show any abnormalities, does not have a decreased probability of recurrent bleeding after hysteroscopy. In contrast, the woman in whom a polyp is diagnosed at hysteroscopy might benefit from the hysteroscopy, but only if removal of the polyp reduces the probability of recurrent bleeding.

The majority of gynaecologists advocates removal of endometrial polyps.<sup>36</sup> It is considered that the removal of endometrial polyps reduces the probability of recurrent bleeding with reported success rates varying between 40% to 100%. However, there still is a lack of high-quality evidence regarding the efficacy of intrauterine polypectomy with respect to abnormal uterine bleeding.<sup>37</sup> Endometrial polyps are highly prevalent in women with PMB<sup>8</sup> and, if causative, may be responsible for significant morbidity. Alternatively we may be subjecting women to unnecessary interventions, risks and wasting valuable health care resources. No studies exist that included a control group when reporting on the efficacy of polypectomy. From this point of view it can be questioned if the diagnosis of endometrial polyps is important and randomized controlled trials on this subject are advocated.<sup>37</sup> Therefore, the recommendation to perform SIS or office hysteroscopy to diagnose benign intrauterine pathology (i.e. endometrial polyps) is not supported by current literature.

The question that remains to be answered is whether endometrial polyps in patients with PMB should be removed when malignancy has been excluded, in view of recurrent bleeding symptoms. On the one hand, this will depend on the prevalence of benign endometrial polyps in patients with PMB, and whether such polyps can be diagnosed accurately, for example with TVU or with SIS. On the other hand, this depends on whether removal of a benign endometrial polyp improves outcome.

## Aims of the thesis

The aim of this thesis is to evaluate the current diagnostic work-up in women with PMB.

## Outline of the thesis

**Chapter 2** studies the preference of patients for diagnostic management of PMB. Women were asked to make a trade-off between expectant management after transvaginal ultrasound or complete diagnostic work-up including invasive diagnostic procedures, i.e. hysteroscopy. This study was performed among women with PMB who had had a hysteroscopy in the diagnostic work-up.

**Chapter 3** determines the diagnostic accuracy of endometrial thickness measurement in the detection of endometrial cancer among women with PMB with individual patient data using different meta-analytic strategies.

**Chapter 4** describes the prevalence of endometrial polyps at hysteroscopy in women with PMB. In addition, it describes the possibility of diagnosis and treatment of these polyps in the same outpatient hysteroscopy session.

**Chapter 5** determines the diagnostic accuracy of endometrial thickness measurement with transvaginal ultrasound for detection of endometrial polyps in women with PMB. Data on endometrial thickness measurement with transvaginal ultrasound and findings at hysteroscopy were combined to perform a receiver operator characteristics (ROC) analysis to assess the discriminative capacity of endometrial thickness for the presence of endometrial polyps.

**Chapter 6** describes current practice of Dutch gynaecologists in polyp removal. This was surveyed by a mailed self-administered questionnaire regarding polyp removal. Gynaecologists were asked about their individual performance of polypectomy: setting, form of anaesthesia, method and instrument used.

**Chapter 7** determines the incidence and significance of recurrent PMB among women diagnosed with an endometrial thickness  $\leq 4$  mm after a first episode of PMB. Patients who presented with PMB were registered prospectively in a multi-center study between January 2001 and June 2003. Diagnostic assessment of the patients followed the Dutch guideline on this subject. For women with endometrial thickness  $\leq 4$  mm we determined whether recurrent bleeding had occurred.

**Chapter 8** estimates the incidence and significance of recurrent PMB among women diagnosed with an endometrial thickness  $> 4$  mm after a first episode of PMB. Patients who presented with PMB were registered prospectively in a multi-center study between January 2001 and June 2003. Diagnostic assessment of the patients followed the Dutch guideline on this subject. For women with endometrial thickness  $> 4$  mm we determined time to recurrent bleeding and diagnosis at recurrent bleeding. Furthermore, we evaluated if incorporation of hysteroscopy or polyp removal at initial work-up had any influence on recurrent bleeding.

**Chapter 9** evaluates the design of a randomized controlled trial in women with PMB and an endometrial polyp. We set up a prospective cohort study with an embedded randomized clinical trial comparing polypectomy and expectant management. We report this study design and its problems and propose a possible alternative study design.

**Chapter 10** summarizes the results of the studies presented in this thesis and gives clinical implications and implications for future research.



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