Postmenopausal bleeding : studies on the diagnostic work-up

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Summary, general discussion and recommendations

Summary

This thesis aims to evaluate the diagnostic work-up for postmenopausal bleeding (PMB) from several viewpoints. We focused on patients' preferences, thereby determining what risk of false reassurance women would consider acceptable to what cost; we investigated whether the diagnosis of benign disease should be incorporated in the initial diagnostic work-up; and we assessed whether the risk of recurrent bleeding is related to the results of initial work-up. This chapter summarize and discusses the findings from our research, furthermore clinical and future research implications are put forward.

The introduction (**chapter 1**) addresses the clinical problem of postmenopausal bleeding. It gives an outline of the diagnostic work-up in women with PMB and presents the aim of this thesis. The problem of PMB has two components: (1) the risk of endometrial carcinoma; (2) diagnosis of benign intracavitary pathology once malignancy has been ruled out.

The role of transvaginal ultrasound (TVU) in the diagnostic work-up of women with PMB to exclude endometrial carcinoma is presented in this chapter. The diagnostic accuracy of TVU was established in three previous meta-analysis and as such is now implemented in guidelines and clinical practice. However, these meta-analyses have come to different conclusions on the diagnostic accuracy of TVU. Furthermore the preference of the patients regarding the diagnostic work-up in case of PMB was never systematically taken into account.

Although guidelines on diagnostic work-up of PMB focus on exclusion of endometrial carcinoma, further diagnostic assessment can be undertaken to diagnose benign intracavitary pathology, mainly endometrial polyps. TVU, Saline Infusion Sonography and hysteroscopy are available to evaluate the uterine cavity for benign endometrial polyps. During SIS or hysteroscopy in women with PMB endometrial polyps are frequently found, but whether or not these polyps are causative of PMB, is not clear. Women suffering from PMB might benefit from uterine cavity evaluation and diagnosis of endometrial polyps, if consecutive removal of endometrial polyps will lead to less recurrent bleeding. However, there is a lack of high-quality evidence regarding the efficacy of polyp removal in women with PMB.

In **chapter 2** we systematically assess patients' preferences for the diagnostic management of PMB. For this purpose we designed a structured interview, which was taken from 39 women who had had an office hysteroscopy in the diagnostic work-up of PMB. Women were informed about the probability of endometrial carcinoma versus benign disease and about advantages and disadvantages of different diagnostic strategies, i.e. expectant management after TVU or complete diagnostic work-up including invasive procedures. Most women wanted to be 100% certain that carcinoma could be ruled out. Only 5% of the women were willing to accept a

more than 5% risk of false reassurance. If the risk of benign disease exceeded 25%, the majority of women would prefer immediate diagnosis and treatment of benign pathology. From this preference study we concluded that women with PMB are prepared to undergo hysteroscopy to rule out any risk on cancer and that women aim for a high accuracy of the diagnostic work-up. This implicates that measurement of endometrial thickness with TVU as a first-line test in the assessment of PMB should be reconsidered.

In **chapter 3** we determined the diagnostic accuracy of endometrial thickness measurement in the detection of endometrial carcinoma among women with PMB. We performed a meta-analysis using individual patient data (IPD) from individual studies. We included data on 2,896 patients of which 259 patients had endometrial carcinoma. Different Receiver Operator Characteristics (ROC) analyses were performed. All these ROC analyses resulted in similar ROC curves, with Area Under the Curve's (AUC) varying between 0.82 to 0.84. These ROC curves indicated a lower AUC than the previously reported meta-analysis using conventional techniques. The commonly used cut-off values of 4 mm and 5 mm were found to have a sensitivity of 95% (95% CI 86.1-98.2%) and 90% (95% CI 80.0-95.5%) respectively. Only a cut-off value of 3 mm, yielded a high sensitivity of 98% (95% CI 90.1-99.6%). We concluded that previous meta-analyses on endometrial thickness measurement have overestimated its diagnostic accuracy in the detection of endometrial carcinoma. However, TVU measurement of endometrial thickness in women with postmenopausal bleeding using a cut-off value of 3 mm is still clinically useful and using such a cut-off value can reliably exclude endometrial carcinoma in women with postmenopausal bleeding.

In **chapter 4** the use of office hysteroscopy in the diagnosis and treatment in women with PMB is described. Endometrial polyps have a prevalence 41% in women with PMB and endometrial thickness > 4 mm. Office hysteroscopy offers the possibility of diagnosis as well as treatment of these polyps. This treatment can be performed in the same session in which endometrial polyps are diagnosed. It was concluded that a decision analysis regarding the diagnosis and treatment in women with PMB is necessary.

In **chapter 5** we determine the accuracy of endometrial thickness measurement with TVU to diagnose endometrial polyps in women with PMB in whom a carcinoma has been ruled out. In women with PMB endometrial thickness was measured with TVU. If endometrial thickness was > 4 mm, office hysteroscopy was performed. At hysteroscopy the uterine cavity was assessed for the presence of endometrial polyps. ROC analysis was performed to assess the capacity of TVU endometrial thickness measurement to diagnose endometrial polyps. We included 178 patients with endometrial thickness > 4 mm of which 90 (50%) had an endometrial polyp. ROC analysis showed an AUC of 0.64. Therefore, we concluded that in women with PMB

in whom carcinoma has been ruled out, measurement of endometrial thickness with TVU is not useful in the diagnosis of endometrial polyps.

In **chapter 6** we evaluate current practice of Dutch gynaecologists in polyp removal. All practicing gynaecologists in the Netherlands in 2003 were surveyed by a mailed self-administered questionnaire about polyp removal. Polyps were commonly removed in an inpatient setting (71%), under general or regional anaesthesia (77%), and under direct hysteroscopic visualization (69%). Gynaecologists working in a teaching hospital removed polyps more often in an outpatient setting compared to gynaecologists working in a non-teaching hospital (39% versus 19%, $p<0.001$). Thus, in the Netherlands outpatient polyp removal is not practiced on a large scale. However, teaching hospitals are more often performing polypectomy in an outpatient setting. Therefore, we expect that there must be tendency towards outpatient hysteroscopic removal of polyps for the future.

In **chapter 7** we determined the incidence and significance of recurrent PMB among women diagnosed with an endometrial thickness ≤ 4 mm after a first episode of PMB. Women with a first episode of PMB and an endometrial thickness ≤ 4 mm were managed expectantly. Of 249 women with endometrial thickness ≤ 4 mm, 25 (10%) women had recurrent PMB with a median time until recurrent bleeding of 49 weeks. Two women with recurrent bleeding turned out to have an endometrial carcinoma (8%) and one woman had malignant melanoma. Time since menopause, age, body mass index, hypertension, diabetes and anticoagulants were not predictive for recurrent bleeding. We concluded that the recurrence after a first episode of PMB managed expectantly is low and cannot be predicted by patient characteristics. Women with recurrent bleeding should be re-evaluated as they bear a considerable risk of carcinoma.

In **chapter 8** we estimated the incidence of recurrent PMB among women who were diagnosed with endometrial thickness > 4 mm after a first episode of PMB. Women with a first episode of PMB and endometrial thickness > 4 mm underwent endometrial sampling. Women with benign endometrial sampling were included for follow-up. After diagnostic work-up 222 women were included for follow-up. During follow-up 47 (21%) women had recurrent PMB, with a median time to recurrent bleeding of 49 weeks. There was no difference with respect to recurrence rate between patients with polyp removal, patients with normal hysteroscopy, and patients with office endometrial sampling alone at the initial work-up. Two patients were diagnosed with atypical endometrial hyperplasia upon recurrent bleeding. From this study, we concluded that the recurrence rate of PMB in women with endometrial thickness > 4 mm is 21%. This recurrence rate is not related to incorporation of hysteroscopy or polyp removal at the initial work-up.

In **chapter 9** we describe the design of a randomized controlled trial to evaluate the efficacy of polyp removal in women with PMB. We designed a trial in which patients with PMB and endometrial thickness > 4 mm undergo hysteroscopy. If during hysteroscopy a polyp was diagnosed, patients were asked to participate in this trial and after informed consent allocated to immediate removal of the polyp or expectant management. This trial suffered from lack of recruitment related both to doctors seeking for informed consent as well as patients unwillingness to participate in this trial. However, a randomized controlled trial on this subject is still necessary to evaluate the efficacy of uterine cavity evaluation in the diagnostic work-up of women with PMB, focussing on benign pathology. Therefore, we propose an alternative design which might be more feasible. In this alternative design patients undergo TVU and office endometrial sampling and in case of benign histology, patients are then allocated to either uterine cavity evaluation (including SIS and hysteroscopy) with removal of endometrial polyps or expectant management. Such a trial seems more feasible, since it is more in line with current clinical practice. A randomized clinical trial on the subject is still warranted to fill this gap in evidence.

General discussion

At present the diagnostic work-up of women with postmenopausal bleeding (PMB) focuses on how (pre)malignancy or benign intrauterine pathology can be diagnosed. This diagnostic work-up is subject of a NVOG guideline[1] which includes a diagnostic algorithm and gives three key recommendations:

1. Expectant management is justified in women with an endometrial thickness ≤ 4 mm.
2. In case of an endometrial thickness > 4 mm office endometrial sampling can reliably diagnose endometrial carcinoma. After office endometrial sampling, Saline Infusion Sonography (SIS) can be performed to diagnose benign intrauterine pathology.
3. In case of persistent or recurrent PMB a diagnostic hysteroscopy with endometrial sampling should be performed.

Expectant management in women with endometrial thickness ≤ 4 mm

Based on the Dutch guideline, transvaginal ultrasound (TVU) is used as a first step in women with PMB to stratify them in having a high versus low probability of endometrial carcinoma.[1] A previous study showed that Dutch gynaecologists adhere in most cases (73%) to the recommendation of expectant management in case of endometrial thickness ≤ 4 mm.[2] The first recommendation of the guideline seems widely implemented. However, the guideline seems to be formulated without a systematic consideration of patients' preferences.[2] It is of clinical importance that guidelines fulfil the expectations of the patient. In chapter 2, we systematically assessed patients' preferences regarding the trade-off between diagnostic accuracy and invasiveness in the diagnostic work-up in case of PMB. Women with PMB appeared to be prepared to undergo a rather invasive and painful diagnostic procedure such as hysteroscopy to rule out any risk on cancer. This finding would imply that, from a patient's point of view, the measurement of endometrial thickness with TVU as a first line test in the assessment of PMB should be reconsidered. However, guidelines represent a broader perspective than the individual patient and from a societal perspective also other factors (including costs) are to be considered.

The Scotland National Health Services emphasizes the woman's input in further investigation if she is thought to be at low risk after TVU: "If the clinician, the patient or both are not satisfied with this level of reassurance, further investigation is justified.[3] This should include an endometrial biopsy to obtain a histological assessment". Before subjecting all women to office endometrial biopsy (Pipelle), one should keep in mind that the failure rate of office endometrial sampling has been reported to be as high as 25% and that in women in whom office endometrial sampling failed, hysteroscopy is advised.[4] A strategy, in which all women undergo office endometrial sampling unconditional upon TVU results, can therefore result in more hysteroscopies in women with PMB. In this way, we may be subjecting women to unnecessary

interventions, risks and wasting valuable health care resources. Cost-effectiveness analyses have shown that a strategy starting with TVU was most cost-effective.[5,6] Only in case of a high disease prevalence (> 10-15%) strategies with office endometrial sampling or hysteroscopy became more cost-effective.[6]

Another aspect of expectant management in women with endometrial thickness ≤ 4 mm is the diagnostic accuracy of TVU. This diagnostic accuracy of TVU in women with PMB has previously been estimated based on individual studies with varying positivity cut-off values as well as meta-analyses of the reported results. [7-13] With respect to meta-analysis of randomized controlled trials, individual patient data (IPD) meta-analysis is considered to be superior over meta-analysis of the literature.[14-16] Meta-analyses using individual patient data instead of published summary data have come to less optimistic, but more accurate, conclusions. Limitations of conventional meta-analysis based on published data, might be overcome by meta-analysis of individual patient data. In chapter 3, we used a meta-analytic approach in which individual patient data from a series of original studies are combined. We showed that in previous studies and meta-analyses the diagnostic accuracy of TVU has been overestimated. We demonstrated a lower diagnostic accuracy for TVU than was reported previously, which resulted in a sensitivity of 95% for a specificity of 47% at a cut-off level of 4 mm. At a cut-off level of 3 mm for endometrial thickness, we found a sensitivity of 98% for specificity of 35%. Therefore, based on the present meta-analysis, the use TVU measurement of endometrial thickness remains justified but we recommend the use of a cut-off level of 3 mm. Such a cut-off value reduces a 10% pre-test probability to a 0.6% post-test probability. Although patients aim for a post-test probability of 0%, such a post-test probability seems virtually impossible. One should keep in mind that the risk of endometrial carcinoma in a population of asymptomatic postmenopausal bleeding is reported to be 0.2%.[17] Although, the use of a cut-off level of 3 mm results in a higher sensitivity which is more in-line with patients' preferences, other diagnostic strategies have to be evaluated. Cost-effectiveness analyses have to be repeated to evaluate whether a strategy starting with TVU and using a cut-off value of 3 mm remains cost-effective as a strategy with TVU using a cut-off value of 4 mm. Alternatively a strategy starting with office endometrial sampling might become more cost-effective.

Another aspect of expectant management in women with endometrial thickness ≤ 4 mm is the chance of recurrent bleeding. In chapter 7 we studied this chance, and showed that recurrent bleeding in patients with PMB occurs in only 10% with a median time to recurrent bleeding of one year. We could not identify patient factors associated with recurrent bleeding. This low recurrent bleeding rate is supportive for the use of TVU as a first test in the work-up for PMB.

Diagnosis of benign pathology

The second recommendation of the NVOG guideline focuses on the diagnosis of benign intrauterine pathology.[1] Endometrial polyps are prevalent (40%) in women with PMB and endometrial thickness > 4 mm (chapter 4 & 9). They are easily diagnosed and removed at office hysteroscopy (chapter 4). Whether or not SIS or an office hysteroscopy (i.e. uterine cavity evaluation) should subsequently be performed in these women is left to the discretion of the individual gynaecologists. A guideline adherence studied showed that in 13 to 17% of the cases, gynaecologists proceeded with hysteroscopy where office endometrial sampling would have been sufficient to exclude malignancy.[2] Uterine cavity evaluation (SIS or hysteroscopy) is often performed in case of PMB and endometrial thickness > 8 mm or suspicion of intracavitary pathology on TVU.[18] However, our study (chapter 5) demonstrates that TVU endometrial thickness measurement has poor discriminative ability for detecting or excluding endometrial polyps and therefore is not clinically useful in the diagnosis of such benign focal pathology. TVU can not reliably detect those patients that have a high probability of focal endometrial pathology and as such can not be used in the work-up for benign pathology.

It can be questioned if the diagnosis of endometrial polyps is of clinical importance. To answer this question, four aspects need to be taken into consideration. First, one can assume that focal carcinomas in an endometrial polyp are only detected if this polyp is removed. The prevalence of serious endometrial disease within polyps is low.[19,20] If endometrial polyps with a focal carcinoma inside the polyp are not removed, it is to be expected that these cancers will become manifest with clinical signs of recurrent PMB and the patient will then undergo another endometrial sampling. Whether this delay in detection of tumors significantly alters the prognosis remains unclear.[21,22] The second argument for diagnosis and removal of endometrial polyps is that women who underwent polypectomy are thought to experience less recurrent bleeding. However it has been shown that (smaller) endometrial polyps may regress spontaneously and as such may not be responsible for PMB.[19,23] Furthermore, endometrial polyps are also found in women without PMB with a prevalence around 10%.[24,25] Alternatively, endometrial polyps may be causative of PMB and removal will therefore lead to less recurrent bleeding. In chapter 8, we showed that the recurrence rate after a first episode of PMB and endometrial thickness > 4 mm is 21%. There was no difference in recurrent bleeding for patients with hysteroscopy and/or dilatation and curettage (D&C) at initial work-up and patients with office endometrial sampling, nor was there a difference between patients with an endometrial polyp diagnosed and treated at initial work-up and patients without a polyp. Unfortunately, D&C was used in this study and D&C has been shown to miss endometrial polyps in 50% to 85% of the cases and as such D&C should not be performed for diagnosis or removal of endometrial polyps.[26,27] Hysteroscopy is generally considered to be superior for endometrial polyp removal. Given the fact that hysteroscopic removal of endometrial polyps was performed in at least part of this group and therefore part of this group was treated adequately, one would still

expect the recurrence bleeding rate to be lower compared to the group without hysteroscopy or D&C. Since this lower recurrence rate was not found, the removal of polyps does not seem to lead to less recurrent PMB and from this point of view diagnosis of polyps whether with SIS or hysteroscopy is not clinically useful. A third argument can be found in patients' preferences regarding diagnosis and treatment of benign pathology. In chapter 2 we found that patients would prefer immediate diagnosis and treatment of endometrial polyps in case the probability of recurrence of bleeding was estimated to be more than 25%. Although the recurrence bleeding rate of 21% lies close to this point, the exact recurrence bleeding rate caused by an endometrial polyp left in situ is still not known. Furthermore, given the present knowledge, this recurrence bleeding rate is not lowered by uterine cavity evaluation (including polyp removal) at first work-up. Uterine cavity evaluation and subsequent polyp removal can be performed at first work-up, however this does not seem to lead to less recurrent bleeding and that is what patients expect if they prefer immediate uterine cavity evaluation.

Although SIS and office hysteroscopy are easily performed, the effectiveness of uterine cavity evaluation (SIS or hysteroscopy) at the initial work-up of PMB should be subject of future studies. Therefore, uterine cavity evaluation for the sole purpose of detecting endometrial polyps in case of PMB has only to be undertaken after counseling the patient about the above mentioned arguments or within study settings.

At present hysteroscopic polyp removal in an outpatient setting is not common practice in the Netherlands (chapter 6). Furthermore, 30% of the gynaecologists will remove endometrial polyps by D&C (chapter 6). D&C has been shown to miss endometrial polyps in 50% to 85% and should therefore not be performed for diagnosis or removal of endometrial polyps.[26,27] Since hysteroscopy under general anaesthesia carries a higher risk of complications than office hysteroscopy, it is questionable if in this clinical setting hysteroscopy has to be incorporated in the work-up of women with PMB.[28] Therefore it is of importance that those gynaecologists that proceed with uterine cavity evaluation (SIS or hysteroscopy) as is stated in the second recommendation of the guideline, do so in an office setting (SIS or office hysteroscopy). Before office hysteroscopic polyp removal becomes widely available, evidence is needed to support the efficacy of polyp removal in case of PMB.

A randomized controlled trial (RCT) is needed, to unequivocally answer the question of efficacy of polypectomy in case of PMB. A trial in which patients with PMB and an endometrial polyp at hysteroscopy were randomized to polypectomy or expectant management, turned out not to be feasible, at least in our setting (chapter 9). The low recruitment in this trial was probably related both to the doctors at the outpatient clinic as well as the patients. Expectant management in case of endometrial thickness ≤ 4 mm or in case of benign histology after endometrial thickness > 4 mm, might be generally accepted.[2] In contrast, expectant management in case

of a hysteroscopically diagnosed polyp is not so easy to accept, neither for patients nor for doctors. The question whether removal of benign endometrial polyps in patients with PMB is effective, remains therefore to be answered. An alternative design of a RCT, as proposed in this chapter, might be more feasible. Until such distinct evidence becomes available, gynaecologists should be hesitant to incorporate hysteroscopy or SIS in the diagnostic work-up of women with PMB.

Diagnostic work-up of women with recurrent PMB

The third recommendation of the NVOG guideline focuses on the work-up of women with recurrent PMB. The chance of recurrent PMB is 10% in women with endometrial thickness ≤ 4 mm at initial work-up and 21% in women with endometrial thickness > 4 mm. At recurrent bleeding endometrial carcinoma was diagnosed in 8% of the women with initial endometrial thickness ≤ 4 mm and in 4.3% of the women with initial endometrial thickness > 4 mm. Therefore, all patients with recurrent PMB should undergo histology sampling to exclude malignancy, irrespective of the initial assessment with TVU. Whether this should be done by hysteroscopy and targeted endometrial biopsy or by office endometrial sampling, is not yet clearly established. It can be argumented that in women in whom only TVU was performed at initial work-up (≤ 4 mm), office endometrial sampling should be performed at recurrent bleeding; whereas in those women in whom already office endometrial sampling was performed, immediate office hysteroscopy with targeted biopsy could be performed. Women with recurrent bleeding are at risk of endometrial carcinoma (4% to 8%) and these women are possibly falsely reassured at initial work-up (false-negatives of initial diagnostic test). Therefore the work-up at recurrent bleeding should consist of a different diagnostic test with a higher diagnostic accuracy. However, precisely how the diagnostic algorithm of women with recurrent bleeding should be, remains to be determined in future research.

Future research

Expectant management in women with endometrial thickness ≤ 4 mm

Future research should focus on the consequences of a cut-off level of 3 mm. A sensitivity of 98% for a specificity of 35% implies that we find 2% more endometrial carcinomas for 15% more invasive diagnostic procedures. What effect this has on cost-effectiveness has to be determined in future research. In this light other diagnostic strategies have to explored, such as a diagnostic strategy starting with office endometrial sampling. Patients and doctors aim for a higher diagnostic accuracy than is presently offered with TVU measurement of endometrial thickness. Such a higher accuracy might be achieved by incorporation of patient's characteristics (e.g. age, presence of diabetes, Body Mass Index (BMI), presence of hypertension) in the diagnostic work-up. The incorporation of TVU with patient's characteristics in a diagnostic strategy has been studied and resulted in higher diagnostic accuracy.[4,29-31] Statistical methods can be used to develop and further improve such models and incorporating patient's characteristics with diagnostic tests.[31,32] Furthermore, by combining and analysing individual patient data from different studies using (IPD meta analyses), larger databases can be obtained, in which previously described models can be externally validated. Such models could be incorporated in clinical prediction rules, where the individual probability for endometrial cancer is obtained for each individual woman, and a diagnostic algorithm is developed to maximize the diagnostic accuracy at an acceptable patient burden and health care costs. Such prediction rules are currently also available in reproductive medicine or similar to a risk of malignancy index. After developing such clinical prediction rules, diagnostic accuracy and clinical applicability should be tested in clinical practice in a prospective multicenter study. If indeed, such a model would lead to higher diagnostic accuracy than TVU alone, office endometrial sampling could then for example be offered only to those women with a high probability of endometrial cancer.

Diagnosis of benign pathology

With respect to benign pathology, future research should focus on the diagnosis and treatment of endometrial polyps in women with PMB. Diagnosis is only useful if treatment is beneficiary. This question still remains to be answered. An RCT in which women were randomized after the diagnosis of endometrial polyps was not feasible. An alternative design in which women are randomized after exclusion of malignancy to either SIS and hysteroscopy or expectant management, seems more feasible, since this is more in line with current practice. Preparations for such a trial are undertaken (POMPOEN-trial). In this trial women with PMB and endometrial thickness > 4 mm undergo office endometrial sampling. In case office endometrial sampling shows benign histology, women are randomized to expectant management or further work-up. If randomized to further work-up, all women undergo SIS and office hysteroscopy; in case endometrial polyps are diagnosed these are then removed. If in the end,

removal of endometrial polyps in women with PMB is shown to be effective (less recurrent PMB), then a diagnostic strategy focussing on exclusion of malignancy and diagnosis and treatment of benign intrauterine pathology has to be developed. The optimal strategy should be based on the diagnostic accuracy, costs and patient burden of different test combinations. Furthermore, the preference of the patient should be taken into account, as the trade-off between accuracy, costs and test burden depends on how patients value each aspect. Although SIS and hysteroscopy have comparable diagnostic accuracy, SIS is reported to be less painful than hysteroscopy.[33,34] However, patient's might be willing to accept more pain and discomfort in exchange for diagnosis and treatment options in one session, such as is offered with hysteroscopy. Further studies should focus on different diagnostic strategies and patients' preferences regarding such strategies.

Ideally, the diagnostic strategy for exclusion of malignancy should be combined with the diagnostic strategy for benign pathology, resulting in a diagnostic algorithm in which exclusion of malignancy and treatment of benign pathology (if this has been proven to be beneficiary) are combined.

Clinical implications

This thesis supports the use of TVU as a first step in women with PMB. However, it advocates the use of a cut-off value of 3 mm instead of the currently used 4 or 5 mm. With a sensitivity of 98% for a specificity of 35%, a cut-off value of 3 mm will reduce a 10% post-test probability of endometrial carcinoma, to a post-test probability of 0.6%. With respect to diagnosis of benign intracavitary pathology (endometrial polyps), this thesis emphasizes the lack of high-quality evidence regarding the diagnosis and removal of endometrial polyps with respect to recurrent PMB. Considering the results of our cohort study in women with PMB, endometrial thickness > 4 mm and benign histology, uterine cavity evaluation (i.e. SIS or hysteroscopy) does not seem to be beneficiary to patients with PMB with respect to recurrent bleeding. Clinicians should therefore be hesitant to routinely incorporate uterine cavity evaluation in the diagnostic work-up of women with PMB with the sole purpose of diagnosing and treating benign pathology. Uterine cavity evaluation (SIS and hysteroscopy) should therefore be performed in trial settings.

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