The diagnostic work-up of women with postmenopausal bleeding
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Citation for published version (APA):
vан Hanegem, N. (2015). The diagnostic work-up of women with postmenopausal bleeding
Chapter 9

General discussion and implications
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General discussion

The work-up of women with postmenopausal bleeding focuses on the exclusion of endometrial (pre) cancers and (possible) diagnosis and treatment of endometrial polyps and can be divided in different stages:

1. Selecting women with a high risk of having endometrial cancer for further diagnostic work-up, by TVS, applying prediction models or adding Doppler features.
2. Invasive diagnostic work-up by endometrial sampling, SIS and/or hysteroscopy.
3. Treatment of women with (recurrent) PMB to prevent recurrent bleeding.

The selection of women with a high risk of endometrial cancer

When a patient presents with PMB the first step in most guidelines is referral to a gynaecologic practice for (vaginal) examination, Pap smear and TVS. Measurement of the endometrial thickness by TVS is an evidence-based method to distinguish between women with a low or high risk of having endometrial cancer. The measurement of endometrial thickness is easy to learn and the inter-observer variability is very low.1 This method is well studied and widely implemented.2-4 It has shown to be accurate in ruling out endometrial cancer, with a risk of endometrial cancer when the test is negative of 0.7–3.5%, depending on the cut-off point used (Chapter 2).

The risk after a negative test (post-test probability) is not only dependent on test characteristics, but also on the pre-test probability, which is altered by patient characteristics. To lower the post-test probability, patient characteristics could be implemented in the diagnostic work-up by implementing prediction models. However, the use of these models is not thoroughly studied and until now only one of the models has been externally validated (Chapter 3 and 4). Therefore, implementation of prediction models in clinical practice is still not possible. The external validation of a model developed by Opmeer et al showed that in situations where no ultrasound is available, women could safely be selected based on their characteristics. However, this is only the case for a very low specificity, which means that many women need to undergo further invasive testing with a small chance of diagnosing a (pre) cancer. In the Dutch case, all gynaecologist have easy access to an ultrasound machine, which instigates that this model is not applicable in the Dutch healthcare system. A model based on patient characteristics would only be useful if the number of invasive procedures could be significantly decreased. By combining patient characteristics
in a prediction model with TVS, the number of women that need further invasive procedures to obtain material for histological assessment can be decreased only slightly, compared to the measurement of endometrial thickness by TVS (Chapter 4). Therefore, this model is also currently not ready to be used in clinical practice.

**Invasive diagnostic work-up**

When a thickened endometrium is diagnosed in women with PMB, further invasive work-up is indicated because of a high risk of having endometrial (pre) cancer. In most guidelines, TVS will be followed by endometrial sampling to obtain histology. Nowadays, hysteroscopy is often used as the next step after endometrial sampling in the diagnostic work-up, but could also be seen as an alternative to endometrial sampling with the advantage of diagnosing and directly removing an endometrial polyp. Although hysteroscopic polypectomy is one of the most frequently performed procedures in gynaecologic practice, the causative relationship between endometrial polyps and (postmenopausal) recurrent bleeding is not proven. In postmenopausal women with a thickened endometrium, only one cohort study is available and this study shows no difference in recurrent bleeding after hysteroscopy versus expectant management, regardless if a polyp was present or not.\(^5\) From our randomised trial we can conclude that operative hysteroscopy does not reduce recurrent bleeding and that costs to prevent one case of recurrent bleeding are quite high (around 29,000 euro). Yet, hysteroscopy detected focal endometrial (pre) cancer in 6% of women was initially missed by endometrial sampling (Chapter 5 and 6). This finding, together with the fact that sensitivity of endometrial sampling is much lower than we thought (Chapter 7), warrants further diagnostic work-up in women with a thickened endometrium and benign histology to diagnose focal endometrial (pre) cancers. Furthermore, endometrial sampling fails in about 40% of cases (because either it is not performed successfully or shows an insufficient sample) and in about 7% of these failed samples an endometrial (pre) cancer is diagnosed. In combination, these findings make us question whether endometrial sampling should still be part of the diagnostic work-up of women with PMB.

Such a diagnostic work-up to diagnose focal endometrial (pre) cancers could involve a strategy with direct hysteroscopy in all women or a strategy with SIS to select women for hysteroscopy with a (high suspicion of) an endometrial polyp. The cost-effectiveness analysis alongside our randomised trial shows that a strategy using SIS to select women for therapeutic hysteroscopy is about 2000-3000 euro less expensive per (pre) cancer detected compared to direct hysteroscopy for all
women. The possible 3000 euro decrease in detecting one endometrial (pre) cancer could be an argument for implementing SIS in the diagnostic work-up. However, these costs are calculated for a setting in a Dutch hospital without the availability of a ‘one-stop’-treatment and therefore these findings cannot be unconditionally generalised for all circumstances.

From current literature, it is unclear whether the diagnostic accuracy of SIS is high enough to select women for therapeutic hysteroscopy. From studies in premenopausal women we know that sensitivity of SIS to detect an abnormal uterine cavity is 95%. We found a sensitivity of 93% and a specificity of 94% for SIS to diagnose endometrial polyps in postmenopausal women (Chapter 5). However, SIS currently cannot be implemented as a standard in guidelines on the diagnostic work-up of women with postmenopausal bleeding, because research on the diagnostic accuracy specifically in postmenopausal women is needed.

Prevention and treatment of recurrent bleeding

The idea behind the design of the randomised trial described in this thesis was that we sought to study the effectiveness of the removal of endometrial polyps on recurrent bleeding. From the results of this study we can conclude that diagnosing focal (pre) cancers should be the indication to perform a hysteroscopy and not the prevention of recurrent bleeding. In the literature, only sparse evidence is available on the prevalence of recurrent bleeding in women who present with PMB. In a Dutch cohort of women with PMB in whom previous investigations have yielded normal findings, the chance of recurrent bleeding was 10% for women with endometrial thickness < 4 millimetres and 21% with endometrial thickness ≥ 4 millimetres. A British study showed a recurrent bleeding rate of 5% in a population of women with PMB and normal findings at initial investigation, regardless of the endometrial thickness.

As the majority of women with recurrent PMB will not have a (pre)cancer, we do not have an effective treatment available for women with recurrent bleeding or an initial episode of PMB to prevent them from returning to the hospital with recurrent bleeding and undergo invasive diagnostic work-up. Women are often diagnosed with ‘atrophic endometrium’ in cases where they present recurrent PMB, a thin endometrium (< 4 mm) and no abnormalities at hysteroscopy. On theoretical grounds, the use of local vaginal oestrogen therapy could prevent recurrent bleeding in women with postmenopausal bleeding caused by ‘atrophy’. For women with initial endometrial thickness > 4 mm and negative hysteroscopy, insertion of LNG-IUD
has been described to have a beneficial effect with respect to recurrent PMB. Furthermore, after LNG-IUD insertion, histological regression of hyperplasia is seen. Given the burden of recurrent PMB for patients and the burden of repeated hysteroscopies, there is a need to establish a safe and effective intervention for women with (recurrent) PMB to prevent recurrent bleeding.

Future research

The selection of women with a high risk of endometrial cancer

The use of prediction models in women who present with PMB should be studied further. Existing models could be adjusted with different thresholds (for example a different threshold for the endometrial thickness) or by the use of different subgroups of patients. It would be useful to implement such a model in clinical practice only if the number of invasive procedures can be reduced without missing endometrial cancers. Furthermore, research should focus on the use of Doppler. Ultrasound machines will be more advanced in the coming years and more hospitals will be able to purchase these advanced machines. Consequently, Doppler will be more widely available. As Doppler is more difficult, with a longer learning curve than the widely used grey-scale ultrasound, measurement of endometrial thickness will most probably always be the first step in ultrasound assessment. And because women with postmenopausal bleeding and endometrial thickness ≥ 5mm have a high risk (1 in 4) of endometrial cancer, it is always necessary to obtain an adequate endometrial sample for histological diagnosis in these women. Obtaining histology can be performed by endometrial sampling or hysteroscopy, which we will discuss later. However, sometimes it is not possible to measure the endometrial thickness with grey-scale ultrasound or it is not possible to obtain adequate histology by endometrial sampling. In these situations, Doppler could be used to select women with a high risk of endometrial (pre) cancer for hysteroscopy. Prediction models using Doppler have been published, but none of these have been externally validated yet. Additionally, Doppler could be used in women with a thickened endometrium to distinguish between women with an endometrial polyp or diffuse thickened endometrium and this could be used to decide for therapeutic hysteroscopy. Therefore, future research should focus on the diagnostic performance of Doppler to diagnose endometrial polyps and on external validation of prediction models using Doppler in women where TVS or endometrial sampling is not possible.
Invasive diagnostic work-up

Further research on the diagnostic work-up of women with PMB should focus on the most cost-effective sequenced combination of tests after performing TVS. As mentioned above, in most guidelines endometrial sampling is currently the next step in the diagnostic work-up after TVS. Endometrial sampling fails in about 40% of women and the sensitivity in women with PMB is much lower than we thought. Because of the risk of endometrial (pre) cancer, these findings warrant hysteroscopy in women with failed endometrial sampling and also in women with benign histology after endometrial sampling to diagnose focal pathology. From this, the question is what strategy is beneficial in what circumstances. Strategies that need to be compared, both from a patient perspective as well as from a cost-effectiveness perspective, are immediate hysteroscopy in all women with PMB and thickened endometrium versus a strategy in which endometrial sampling and SIS and hysteroscopy are combined, in different sequences and different time-paths (‘one-stop’ versus multiple consultations).

The decision about whether further diagnostic work-up for endometrial polyps and possible focal (pre) cancer is necessary is strongly dependent on the prevalence of endometrial (pre) cancer in the population. Compared to the prevalence known in the literature (5-10% in a population of women with PMB), a 6% prevalence in a pre-selected population of women with PMB and a benign result of endometrial sampling seems quite high. Most existing studies on the prevalence endometrial (pre) cancer in a polyp included a combination of pre- and postmenopausal women in mostly small retrospective cohorts of around 100 to 150 women. Because the diagnostic accuracy of a test is strongly dependent on the pre-test probability (prevalence) and the prevalence of endometrial (pre) cancer is much higher in postmenopausal versus premenopausal women, it is important to study large cohorts with postmenopausal women only. We suggest a large prospective cohort study in which all women with PMB and an endometrial thickness of > 4 mm undergo endometrial sampling, SIS and (diagnostic/therapeutic) hysteroscopy. Through this study, we will be able to investigate the prevalence of endometrial (pre) cancer in a polyp in the Netherlands. Furthermore, diagnostic accuracy and costs-effectiveness of different diagnostic pathways could be studied.

If the indication is set for further diagnostic work-up to diagnose focal pathology, one has to decide between direct hysteroscopy or hysteroscopy preceded by SIS. Because more research on the diagnostic accuracy of SIS in postmenopausal women
is needed, it would be interesting to perform a systematic review on the diagnostic accuracy of SIS to diagnose endometrial polyps specifically in women with PMB. The second knowledge gap on the use of SIS is the sequence in which different diagnostic tests should be done. It would be most cost-effective and patient-friendly if the SIS would be performed during the first contact with the gynaecologist, together with TVS and endometrial sampling. However, we do not know what the effect is on the accuracy of the tests in case these two are combined. Hypothetically, the fluid could affect the quality of the aspiration, when endometrial sampling is performed after the SIS. Also, performing an endometrial sample first could affect the quality of the ultrasound image of the SIS. 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. This study was performed in a mixed population of pre- and postmenopausal women. The optimal sequence of TVS and SIS in combination with endometrium sampling specifically in women with PMB needs to be elucidated. Therefore, we suggest a randomised trial in which patients with PMB are randomly allocated for either SIS and subsequent endometrial aspiration, or in the reverse order. As a primary outcome for this study, we suggest the quality of the endometrial sampling, with the quality of the ultrasound image and pain during the procedures as secondary outcomes.

Prevention and treatment of recurrent bleeding

Because only sparse evidence is available on both prevalence and treatment of recurrent bleeding in postmenopausal women, these aspects should be subject for further research. As we proposed a large cohort study of women with postmenopausal bleeding, we could study the prevalence of recurrent bleeding in this cohort. Furthermore, it would be interesting to study the prevalence of recurrent bleeding in different populations. Regarding the treatment of recurrent bleeding, research should focus on the medical or hormonal treatment of women with PMB where an endometrial carcinoma has been ruled out. To study the effectiveness of hormonal treatment of women with recurrent PMB, we suggest a multi-arm randomised trial:

1. Women with a first episode of postmenopausal bleeding, where endometrial cancer has been ruled out, with a thin endometrium. Randomisation between local vaginal oestrogen therapy and expectant management.
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2. Women with a first episode of postmenopausal bleeding, where endometrial cancer has been ruled out, with a thickened endometrium. Randomisation between LNG-IUD placement and expectant management.

3. Women with a first episode of recurrent PMB where endometrial cancer has been ruled out, with a thin endometrium. Randomisation between local vaginal oestrogen therapy and expectant management.

4. Women with a first episode of recurrent PMB where endometrial cancer has been ruled out, with a thickened endometrium. Randomisation between LNG-IUD placement and expectant management.

The primary outcome of this study should be recurrent PMB within one year and secondary outcomes should be endometrial (pre) cancer, cost-effectiveness, side effects and quality of life.

Clinical implications

The results of the research presented in this thesis supports further diagnostic work-up and treatment of endometrial polyps in women with PMB and a thickened endometrium, because of the risk of an underlying endometrial (pre) cancer. The question that remains is concerned with what the most (cost) effective diagnostic pathway is to diagnose and treat these polyps. 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. Clinicians should therefore be hesitant to routinely incorporate hysteroscopic evaluation in all women with a thickened endometrium. Uterine cavity evaluation (SIS and hysteroscopy) should be performed in a trial setting to gain more knowledge on the prevalence of endometrial (pre) cancer, recurrent PMB and the most (cost) effective diagnostic work-up. On theoretical grounds, SIS should be used to select women with PMB for therapeutic hysteroscopy, after TVS and endometrial sampling.
References


