The diagnostic work-up of women with postmenopausal bleeding

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Chapter 3

Prediction models in women with postmenopausal bleeding: a systematic review

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Abstract

Postmenopausal bleeding is associated with an elevated risk of having endometrial cancer. The aim of this review is to give an overview of existing prediction models on endometrial cancer in women with postmenopausal bleeding. In a systematic search of the literature, we identified nine prognostic studies, of which we assessed the quality, the different phases of development and their performance. From these data, we identified the most important predictor variables. None of the detected models completed external validation or impact analysis. Models including power Doppler showed best performance in internal validation, but Doppler in general gynaecological practice is not easy accessible. We can conclude that we have indications that the first step in the approach of women with PMB should be to distinguish between women with low risk versus high risk of having endometrial cancer and the next step would be to refer patients for further (invasive) testing.

Introduction

Endometrial cancer is the most common gynaecologic cancer. Approximately 95% of women with endometrial cancer present with postmenopausal bleeding (PMB).[1, 2] PMB signals endometrial cancer, which is present in about 10% of cases,[3, 4] or less serious conditions, such as benign endometrial polyps or endometrial atrophy.[3, 5-7]

To reduce invasive procedures in women with PMB, measurement of the endometrial thickness is used to stratify women into low versus high risk of having endometrial cancer. Measurement of endometrial thickness has shown to be accurate in excluding endometrial cancer, although the risk of endometrial cancer with a negative test is still 0.7-3.5% depending on the cut-off point used.[8, 9]

In women with PMB there is considerable variability in endometrial thickness and the likelihood of endometrial cancer.[10] Individual patient characteristics including age, time since menopause, obesity, hypertension, diabetes mellitus and reproductive factors, are associated with a higher risk of endometrial cancer.[10-16] While the probability of postmenopausal bleeding decreases with increasing age,[17] the probability of endometrial cancer in women with PMB increases significantly with increasing age. The probability rises from 1% in women younger than 50 years to 24% in women older than 80 years.[18]

In clinical practice, tests are commonly combined in diagnostic sequences and disease probabilities are usually estimated in a hierarchical manner: first combining information from history and examination, followed by additional information obtained from diagnostic tests. The post-test probability is not only dependent on test characteristics but also on the pre-test probability, which is altered by patient's characteristics. However, current diagnostic policy in women with PMB is not based on these patient specific risk factors, but only on one fixed cut-off point for endometrial thickness.[2, 19-21]

Clinical doctors want to identify women with a high risk for endometrial cancer when presenting with PMB. Several articles have studied this subject and developed models to estimate the individual chance of endometrial cancer in women presenting with PMB. The purpose of this review is to give an overview of the existing prediction models for endometrial cancer in women with PMB, to assess their quality and to identify important predictor variables.

Methods

Study identification

We performed a computerized MEDLINE and EMBASE search to identify all studies on prediction models in women with postmenopausal bleeding published from inception to June 2011. The search was limited to human studies, no restrictions were held concerning publication year or language. We included articles reporting on multivariable models predicting endometrial cancer in women with PMB. We checked references cited in the selected articles for further relevant prediction models not identified by the electronic searches. We used all known synonyms for the terms 'postmenopausal bleeding' and 'endometrial cancer' and we used a search-filter for prediction models.[22] The search strategy can be found in Appendix 1.

Study selection

This review focused on articles that report on a prediction model for endometrial cancer in women with PMB. In this review, a prediction model was defined as a multivariable model that expresses the chance of endometrial cancer as a function of two or more predictor variables. PMB was defined as vaginal bleeding after more than one year of amenorrhea after the age of 40 or persistent (>3 months) unscheduled bleeding on hormone replacement therapy (HRT). Two independently working reviewers (NvH and MB) selected the articles, by assessing titles and abstracts. If there were any doubts about eligibility after reading title and abstract, we read the full text version to make sure no articles were missed. In case of disagreement the article was included for full text reading and assessed by a third reviewer (AT).

Study quality assessment

A framework for quality assessment was developed based on the recommendations of Hayden et al[23] and on a quality assessment framework for prediction models in subfertile women to predict the chance of pregnancy.[24] The framework was divided into four sections: study participation, predictor variables, outcome measurement and analysis. Each item in the different sections was scored with 'yes', 'no' or 'unclear'.

Predictor variables

All predictor variables were collected for each prediction model. The predictor variables are the potential predictors, which were tested, both during model development and in the final model. The original articles selected multiple variables or risk factors,

which are thought to be associated with an increased risk of endometrial cancer. These variables have been tested in the original articles for univariate association and, if sufficiently contributing to predictive accuracy in multivariable regression analysis, combined to construct a clinical prediction model. We collected all different predictor variables from the original articles, together with their significance, to identify the most important predictor variables for endometrial cancer. The most important predictor variables had been considered as statistically significant input variables in three or more studies or were considered statistically significant in two studies and had not been tested in other studies.

Model development assessment

The development of a prediction model consists of three phases: model derivation, model validation and impact analysis.[25] In the first phase, model derivation, predictor variables are identified by logistic regression. Model validation, the second phase, consists of an internal and external validation phase.[24] In internally validated models, the performance of the model is tested in the same data set in which the model was developed, or in a group of subsequent patients within the same centre. In external validation, the goal is to demonstrate generalizability and reproducibility in patients different from the patients used for derivation of the original model. Therefore, the prediction model is evaluated on new data collected from an appropriate patient population in a different centre.[26] The final phase of model development is impact analysis, in which prediction models are tested for their ability to change clinician's decisions and to change patient outcomes.[27] All prediction models identified in this review are classified into the different phases of model development. We sent an email to all authors of the identified articles to investigate if their models are undergoing external validation and are not published yet.

Model performance

Performance measures (calibration, discrimination and clinical usefulness) and the range of probabilities given by the different prediction models were recorded. Calibration refers to the agreement between observed probabilities and predicted probabilities for groups of patients; this is usually reported as a calibration plot or a Hosmer-Lemeshow statistic (test for 'goodness-of-fit').[28] Discrimination is commonly reported as the c-statistic (concordance), also referred to as the Area Under the receiver-operating characteristic Curve (AUC). It measures the ability of a prediction model in separating patients with endometrial cancer and patients without

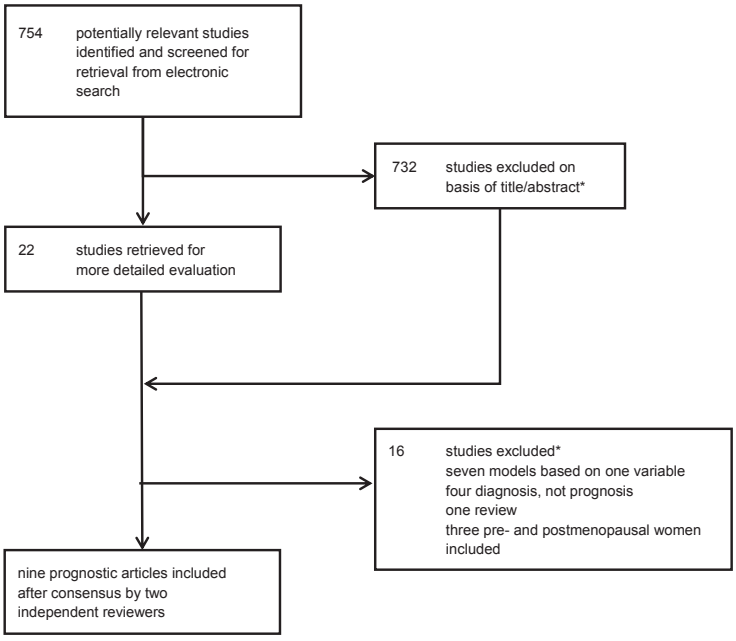
endometrial cancer. An AUC of 0.5 describes a non-informative test, whereas an AUC of 1.0 represents a test that discriminates perfectly between presence and absence of a disease.[29] Clinical usefulness measures how close a prediction for an individual patient is to her actual outcome. This is mostly reported as accuracy (percentage of patients correctly classified), sensitivity or specificity, positive or negative predictive value (PPV or NPV) or likelihood ratios (LR) of a prediction model.[30] As we are interested in identifying a group of patients with a high risk for endometrial cancer, we are most interested in a high sensitivity, high NPV and a low negative LR.

Results

Study identification and selection

Of 754 articles identified by the MEDLINE and EMBASE search, a total of nine articles met the inclusion criteria of our review.[31-39] We identified another three articles by scanning the reference lists of included articles,[40-42] however none of these matched our inclusion criteria after reading the abstract and full text version of these articles (Figure 1).

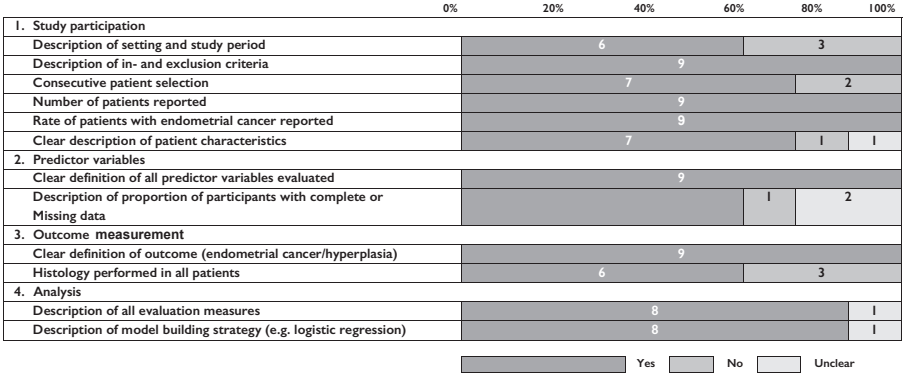
Figure 1. Study selection diagram



Study characteristics

Study characteristics are shown in Table 1. Of the nine selected articles on prediction models for women with PMB, five articles described the development of one model and four articles described two or more different prediction models. In the nine selected articles, four models were based primarily on patient characteristics,[31, 34, 36, 38] four prediction models were based on a combination of patient characteristics and grey-scale transvaginal sonography (TVS) findings,[31, 33, 36] two prediction models were based on a combination of patient characteristics, hysteroscopy and/or grey-scale TVS findings,[31] two prediction models were based on TVS findings only[37, 39] and three models used Doppler TVS findings as a predictor variable.[35, 37, 38] Patient selection and inclusion criteria were not the same in all articles. All nine articles included women with PMB, but three of these articles studies a population of women with a high risk profile for endometrial cancer, based on a endometrial thickness of ≥ 5mm.[35, 37, 38]

Figure 2. Quality of included studies



Study quality

The results of the quality assessment are reported in Figure 2. Overall, study quality was good. The quality of the description of the setting and study period was rated as moderate; this was not described in three out of nine articles. Three articles included all women with postmenopausal bleeding, but performed histology only in patients with an increased endometrial thickness. All three articles explained that no further investigations were performed in women with an endometrial thickness less than five mm, because evidence suggests a very low probability of cancer below this threshold.[33, 34, 36]

Table 1. Study characteristics of included articles

First author, year	Patients	Exclusion criteria	N	N malignancy (%)	Age (years)	Study design	Outcome	Prediction model
Epstein 2002	PMP bleeding, ET ≥ 5mm	Doppler artefacts, incorrect processing	83	16 (19%)	Mean 66	Prospective cohort	Endometrial cancer	2 models: both combination patient history, TVS and Doppler
Randelz-hofer 2002	PMP bleeding	HRT/Tamoxifen use	321	95 (30%)	47-91 (median 68)	Prospective cohort	Endometrial cancer	1 model: TVS only
Bachmann 2003	PMP bleeding, unscheduled bleeding on HRT	-	428	19 (4.6%)	28-61 (median 54)	Prospective cohort	Endometrial cancer	4 models: patient history, patient history + US, patient history + hyst, patient history + TVS + hyst
Bruchim 2004	PMP bleeding	HRT use	95	9 (9.5%)	46-94 (mean 60)	Cohort*	Endometrial cancer	1 model: patient history + TVS
Opmeer 2006	PMP bleeding	History of hysterectomy, HRT use, recurrent bleeding, TVS not possible/ not performed	540	56 (10.3%)	37-91 (mean 62)	Prospective cohort	Endometrial cancer or precancer	2 models: patient characteristics and one combined model with patient characteristics and TVS
Opolskiene 2007	PMP bleeding, ET ≥4.5 mm	Fluid in cavity, absence of power Doppler signals, large myomas, no histologic diagnosis	120	30 (25%)	*	Prospective cohort	Endometrial cancer	Many models: TVS and Doppler
Burbos 2010	PMP bleeding	Asymptomatic women	3047	-	35-97 (median 59)	Prospective cohort	Endometrial cancer	1 model: patient history + TVS
Burbos 2011	PMP bleeding	History of hysterectomy, asymptomatic women	3548	201 (6%)	54-73	Prospective cohort	Endometrial cancer	1 model: patient history only
Opolskiene 2011	PMP bleeding, ET ≥4.5 mm	Absence of processed ultrasound images or reliable histologic diagnosis	261	63 (24%)	47-91 (median 67)	Prospective cohort	Endometrial cancer	4 models: one based on patient history, 1 patient history + TVS, 2 patient history + TVS + Doppler

PMP = postmenopausal
ET = endometrial thickness
CH = cohort study
Hyst = hysteroscopy (pos/neg)
TVS = transvaginal sonography
HRT = hormone replacement therapy

* not well described

Predictor variables

The nine included articles investigated 27 different possible prediction variables (Table 2). Age was tested in all nine articles, turned out to be statistically significant in multivariable analysis in six articles and was used in the prediction model in six articles. Endometrial thickness was tested in eight articles, statistically significant in multivariable analysis in eight articles and used in eight prediction models. Most important predictor variables in patient history were: age, body mass index (BMI), diabetes, frequency of bleeding, use of anticoagulants and HRT. Endometrial thickness, endometrial morphology and endometrial border were identified as significant grey-scale TVS variables. In the three articles studying the use of Doppler for predicting endometrial cancer, endometrial colour score and vascularity index were identified as the most important predictor variables.

Phases of model development

All articles selected in this review addressed the first phase of developing a prediction model: model derivation.[24] Of the nine articles on predicting endometrial cancer in women with PMB, eight had been internally validated but none of these models passed the external validation phase. We asked all six research-groups, which developed the nine different prediction models if their models are undergoing external validation and we received response from all six research-groups. The two prediction models of Opolskiene et al,[37, 38] are undergoing temporal validation (internal validation in a newly recruited patient group) and external validation in an international multicentre study by Valentin et al No results are available yet, since they are still recruiting patients for these studies. The two prediction models developed by Burbos et al[33, 34] were recently used in an article to compare the performance in internal validation of these models.[43] This group is working on external validation. Finally, we can report that the prediction model of Opmeer et al[36] is currently being externally validated in two cohorts: one cohort in three different hospitals in the Netherlands and one in Skåne University Hospital Malmö in collaboration with the group of Valentin et al, but this external validation is not published yet. There were no impact analysis studies, i.e. studies that showed that the prediction model indeed improved patient outcome or was cost-effective in clinical practice.

Performance of the prediction models

The performance of the eight articles that were internally validated their models is presented in Table 3.[31, 33-39] Calibration was described in one article.[39] The estimated

probability of cancer and the observed proportion of patients with endometrial cancer are mentioned in Randelzhofer et al[39] However, calibration is generally reported as a calibration plot. None of the studies reported on calibration in a calibration plot. Discrimination was studied in seven out of eight articles by calculating an AUC. The AUC varied from 0.66 to 0.92 for different prediction models, with the highest AUC for a model combining Doppler and grey-scale TVS.[37] In all internally validated studies clinical usefulness is described, with the highest sensitivity and the lowest negative LR for a combined model with patient characteristics, grey-scale TVS and Doppler.[38] The highest NPV found for a model was 0.996 for a model, which combined patient history, endometrial thickness and histology in a sequential strategy.[36] The performance of the four models using only patient characteristics showed a high sensitivity or high NPV in two models[36, 38] and a low LR for a negative outcome in one model.[38] All three studies in which Doppler was studied as a predictor variable, reported this information to contribute to the prediction of endometrial cancer in women with PMB.[35, 37, 38] Endometrial thickness was used as a variable in eight prediction models and seven found that incorporating endometrial thickness may improve diagnostic accuracy of a model.

Discussion

We systematically reviewed existing prediction models for endometrial cancer in women with PMB and to identify the most important predictor variables. We found nine studies reporting on the development of prediction models for endometrial cancer in women with PMB. Eight of these studies described at least one aspect of internal validation and until now, none of the prediction models have been externally validated.

The different predictor variables can roughly be divided into four subjects: patient characteristics, grey-scale ultrasound variables, Doppler ultrasound variables and hysteroscopy variables. Most prediction models used a combination of these subjects to predict the chance of endometrial cancer. We chose to limit our list of most important predictor variables to those, which had been considered as statistically significant input variables in three or more studies and to those, which were significant input variables in two studies and had not been tested in other studies. By doing this, we identified the most important variables, without missing possible important variables, which have not yet been extensively studied. Using

these limits we identified 11 important input variables for predicting endometrial cancer in women with PMB (Table 2).

Almost all articles reported performance in terms of discrimination and/or clinical usefulness, whereas calibration was reported only incidentally. In this study, we identified five articles describing a prediction model with good discrimination (AUC of >0.8).[31, 35-38] Because only one study described data on calibration, there is insufficient data available to draw conclusions on calibration.

Two studies showed best performance regarding discrimination and clinical usefulness: Opolskiene et al 2011 and Opmeer et al 2007. In the model by Opolskiene et al 2011, a combination of patient characteristics, grey-scale TVS and Doppler was used. They concluded that their model excludes endometrial cancer reasonably well when power Doppler is added. Furthermore, in all three studies that used Doppler, Doppler was found to contribute to the prediction of endometrial cancer in women with PMB.[35, 37, 38] Based on this, we could conclude that the best model in predicting endometrial cancer is a model, which uses a combination of patient characteristics, endometrial thickness and power Doppler. However, power Doppler cannot be used in all patients. All three Doppler-models excluded patients based on different reasons: Doppler artefacts, incorrect processing of TVS image, fluid in the cavity and absence of Doppler signals or large myomas. Another limitation in the use of power Doppler is that these studies do not give information on the interobserver variability and learning curve in measuring Doppler variables. For application of results found in Doppler studies, it is important to use the same ultrasound system, as the colour content of a power Doppler scan depends heavily on Doppler sensitivity.[38]

Although the performance of the models using Doppler seems reasonable, a model using patient characteristics and endometrial thickness might be more useful in daily practice. In a health care system with general practitioners referring patients with a high risk of malignant disease to a specialist, the best model would be a model that can distinguish women with a high risk of endometrial cancer from women with a low risk based on patient characteristics only. Such a model would also be useful in situations where TVS is not directly available. Only women with a high risk could be referred for TVS or to the gynaecologist for a further evaluation and women with a low risk could be reassured and referred only at recurrent bleeding. Based on this review we couldn't identify a model with a good performance in internal validation based on patient characteristics only. However, two of four models based on patient characteristics showed good performance in clinical usefulness with a high sensitivity, a high NPV and/or a low LR for a negative outcome.[36,38] Based on these results we

can conclude that although these models do not show a high AUC, they could be useful in clinical practice. These models were found to discriminate women with a high risk for endometrial cancer from women with low risk and to select women for further (invasive) testing.

The conclusions above are based on reported model performance based on internal validation only. To implement a prediction model into clinical practice, external validation is essential. McGinn et al describe three reasons.[25] A prediction model may reflect associations between given predictors and outcomes that are primarily due to chance. Secondly, the predictor variables used in a model may be idiosyncratic to that specific population, which suggests that the prediction model may fail in a new setting. And thirdly, clinicians may fail to implement the model comprehensively or accurately in their clinical practice. The result would be that a model succeeds in theory, but fails in practice. For a successful implementation, a model should be validated both internally and externally and finally go through the phase of impact analysis in the same population in which a model is derived. As none of the prediction models have completed the phase of external validation, they cannot be used in clinical practice yet.

When evaluating these prediction models by external validation or finally in impact analysis, one should keep in mind that these models were developed in different patient populations. The target population in which a model is derived should be the same as the population in which a model is tested or clinically used. Selecting a high-risk population (for example, a population with an ET ≥ 5mm) will result in a different performance and possibly in the selection of different predictor variables compared to an unselected population of women with PMB. Furthermore, in an unselected population there could be implicate selection dependent of a population within a general practice or a population within a gynaecological practice or differences in health systems in different countries. Different populations have different prevalence of endometrial cancer, which could be an explanation for the differences found in the performance of the models. A consensus has not been found in systematic reviews or in international guidelines regarding the best sequence of diagnostic procedures for women with PMB.[9] Considering the performance of the existing prediction models, we can conclude that we have indications that the first step in the approach of women with PMB should be to distinguish between women with low versus increased risk of having endometrial cancer and the next step would be to refer patients for TVS or further invasive testing.

Table 2. Predictor variables evaluated and used in the prediction models

	Epstein 2002	Randelzhofer 2002	Bachmann 2003	Bruchim 2004	Opmeer 2006	Opolskiene 2007	Burbos 2010	Burbos 2011	Opolskiene 2011
Patient history variables									
Age	3	2	1	1	1	2	1	1	1
BMI					1		1	1	3
Diabetes			3		1		1	1	3
Frequency of bleeding							1	1	
Amount of bleeding							3	3	
HRT use	1		1			3	3	3	1
Anticoagulant use					1				1
Nulliparity					1				3
Time since menopause	3			2					
VAS-score									1
Examiner	3								
Hypertension			3		2		2	2	3
Thyroid dysfunction					3				3
History of cancer					3		2	2	
Ultrasound variables – grey-scale									
Endometrial thickness	1	1	1	1	1	1	1		1
Heterogeneous echogenicity/morphology	1	1				1			
Endometrial border		1				1			
Endometrial fluid in cavity		3							
Endometrial area	2								
Ultrasound variables – Doppler									
Vascularised area	2					1			
Endometrial colour score	1								1
Irregular branching						1			
Vascularity index	1								1
Mean intensity of pixels in endometrial area	2								
Mean intensity of pixels in vascularised area	3								
Hysteroscopy variables									
Suspicious hysteroscopy findings			1						

1 = statistically significant in multivariate analysis and included in model
2 = statistically significant in univariate analysis and not included in model
3 = not statistically significant and not included in prediction model

Table 3. Evaluation of model development and model performance

			Specification of model performance at internal validation			
First author, year	**Development phase**	**Prediction model**	**Discrimination#**	**Calibration**	**Clinical usefulness**	**Result as reported in paper**
Epstein 2002	Internal validation	Subjective prob of cancer (PH, TVS, Doppler) Objective prob of cancer (PH, TVS, Doppler)	0.88 0.88	- -	Sens 0.75, Spec 0.96 Sens 0.88, Spec 0.81	Power Doppler can contribute to diagnosis of endometrial cancer.
Randelzhofer 2002	Internal validation	ET+endometrial structure + myometrial border (cut-off point ET>10mm)	-	Estimated prob 2.8% vs. 2.1% real malignant	Sens 0.97, Spec 0.62 NPV 0.98, Accuracy 0,72	The combined assessment of ET and endometrial morphology may improve diagnostic accuracy.
Bachmann 2003	Internal validation	PH PH+ET PH+hysteroscopy PH+ET+hysterscopy	0.8 0.82 0.910 0.914	-	-	Not much increased value in testing with ultrasound, if hysteroscopy was already performed.
Bruchim 2004	Model derivation	ET+time since menopause	-	-	-	Time since menopause and ET can define when invasive testing is needed.
Opmeer 2006	Internal validation	PH PH+TVS if prob>4% PH+TVS, histology if prob >4%	0.76 0.76 0.9	-	NPV 0.990 Efficiency +0.6 NPV 0.990 Efficiency -0.16 NPV 0.996 Efficiency -0.05	Compared with US only, efficiency gain is reflected in increased AUC and reduced number of procedures, with PH+US in a sequential strategy.
Opolskiene 2007*	Internal validation	ET, echogenicity (and Doppler)	0.91 / 0.92	-	Sens 0.93/0.87 Spec 0.79/0.83 LR- 0.1 / 0.2	A model including ET and heterogeneous echogenicity of the endometrium was best in predicting endometrial cancer, with Doppler diagnostic performance improved marginally
Burbos 2010	Internal validation	DEFAB: diabetes, ET, frequency of bleeding, age and BMI (DEFAB ≥3)	0.77 / 0.66	-	Sens 0.82 Spec 0.50 Accuracy 0.52 LR- 0.36	Fair accuracy in separating women without cancer from women with cancer.

Table 3. Continued

			Specification of model performance at internal validation			
First author, year	**Development phase**	**Prediction model**	**Discrimination#**	**Calibration**	**Clinical usefulness**	**Result as reported in paper**
Burbos 2011	Internal validation	FAD 31: frequency of bleeding, age, diabetes, BMI cut-off 31 (cut-off FAD 31 ≥4)	0.73 / 0.66	-	Sens 0.80 Spec 0.51 Accuracy 0.53 LR- 0.39	Reasonable discriminatory ability.
Opolskiene 2011	Internal validation	PH PH+ET PH+ET+Doppler(VAS) PH+ET+Doppler(VI)	0.74 0.82 0.89 0.91	- - - -	Sens 0.89, LR- 0.22 Sens 0.84, LR- 0.24 Sens 0.70, LR- 0.31 Sens 0.89, LR- 0.14	Fairly good in excluding endometrial cancer when power Doppler is added.

Prob = probability; PH= patient history;
TVS= transvaginal ultrasound; ET = endometrial thickness

* as many models are described we selected the model with the best performance
# discrimination is reported as AUC of the ROC curve

Future perspective

The prediction models that have been developed for women with postmenopausal bleeding showed good performance but have only reached the phase of internal validation. Future research should focus on external validation and impact analysis of these prediction models. We hope that these will confirm their prognostic abilities, so that in the next few years, prediction models can be implemented in general gynaecological practice. Based on this review, we conclude that clinical prediction models show promising results, but further external validation is required as well as impact analysis to maximise diagnostic accuracy of the models at an acceptable patient burden and for acceptable health care costs.

Appendix 1

Search strategy – MEDLINE

#	Searches
1.	postmenopause [mesh]
2.	postmenopau* [tw]
3.	post-menopau* [tw]
4.	#1 OR #2 OR #3
5.	hemorrhage [tw]
6.	bleed* [tw]
7.	hemorrhag* [tw]
8.	haemorrhag* [tw]
9.	blood loss* [tw]
10.	#5 OR #6 OR #7 OR #8 OR #9
11.	endometrial neoplasms [mesh]
12.	endometrial neoplasm* [tw]
13.	endometrial cancer* [tw]
14.	endometrial cancer* [tw]
15.	endometrial malignanc* [tw]
16.	endometrial tumo* [tw]
17.	corpus uteri cancer* [tw]
18.	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
19.	endometrial hyperplasia [mesh]
20.	endometrial hyperplasia* [tw]
21.	#19 OR #20
22.	#18 OR #21
23.	predict* [tiab]
24.	clinical* [tiab]
25.	outcome* [tiab]
26.	risk* [tiab]
27.	#23 OR #24 OR #25 OR #26
28.	#4 AND #10 AND #22 AND #27

Search strategy – EMBASE

#	Searches
1.	postmenopause/
2.	(postmenopau* or post-menopau*).tw.
3.	(after menopaus* or after the menopaus* or following menopaus* or following the menopaus*).tw.
4.	or/1-3
5.	exp bleeding/
6.	(bleed* or hemorrhag* or haemorrhag* or blood loss*).tw.
7.	or/5-6
8.	endometrial neoplasms/
9.	endometrial neoplasm* or endometrial cancer* or endometrial cancer* or endometrial malignanc* or endometrial tumo* or corpus uteri cancer*).tw
10.	or/8-9
11.	endometrial hyperplasia/
12.	endometrial hyperplasia.tw.
13.	or/11-12
14.	10 or 13
15.	(predict* or clinical* or outcome* or risk*).ti,ab.
16.	4 and 7 and 14 and 15

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