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

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# 3

## **Meta-analysis of endometrial thickness measurement for detecting endometrial cancer in women with postmenopausal bleeding: a different approach using individual patient data**

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## Abstract

*Objective:* To determine the diagnostic accuracy of endometrial thickness measurement in the detection of endometrial cancer among women with postmenopausal bleeding (PMB) with individual patient data using different meta-analytic strategies.

*Methods:* We identified studies reporting on endometrial thickness measurements and endometrial carcinoma in women with PMB. Several approaches were used in the analyses of the acquired data. First, we performed Receiver Operator Characteristics (ROC) analysis per study, resulting in a summary Area Under the ROC Curve (AUC) calculated as a weighted mean of AUCs from original studies. Second, individual patient data were pooled and analyzed with ROC analyses irrespective of study, with standardization of distributional differences across studies using multiples of the median and by random effects logistic regression. Finally, we also used a two stage procedure, calculating sensitivities and specificities for each study, and using the bivariate random effects model to estimate summary estimates for diagnostic accuracy.

*Results:* We contacted 79 primary investigators to obtain the individual patient data of their reported studies, of which 13 could provide data. Data on 2,896 patients, of which 259 had carcinoma, were included. All different ROC analyses resulted in rather comparable ROC curves with AUCs of 0.82 and 0.84 respectively, and summary estimates for sensitivity and specificity located along these curves. These curves were indicated a lower AUC than previously reported meta-analyses using conventional techniques.

*Conclusion:* Previous meta-analyses on endometrial thickness measurement have overestimated its diagnostic accuracy in the detection of endometrial carcinoma.

## Introduction

Since two decades transvaginal ultrasonography (TVU) has become widely used in the evaluation of women with postmenopausal bleeding (PMB). Before TVU was introduced in the early 1990s, women with PMB were scheduled for dilatation and curettage (D&C). The goal of TVU assessment of the endometrium is to exclude endometrial carcinoma. In case of a thin endometrium, the chance of endometrial carcinoma is considered to be low and expectant management can be recommended, thus preventing endometrial sampling with D&C or office endometrial biopsy in these patients. In case the endometrial thickness is thickened, additional endometrial sampling is warranted.<sup>1-5</sup>

Different guidelines in various countries advise measurement of endometrial thickness by TVU as a first step in the evaluation of women with PMB.<sup>1-5</sup> These guidelines mostly refer to the meta-analysis of Smith-Bindman *et al.*<sup>6</sup> Two other meta-analyses on this subject are rarely referred to in guidelines.<sup>7,8</sup> Similarly, the meta-analysis by Smith-Bindman *et al.*<sup>6</sup> is the most cited publication (total citation 169 by Web of Science) compared to the other two meta-analyses (citations of 37 and 37 respectively by Web of Science).<sup>7,8</sup> The meta-analysis of Smith-Bindman *et al.*<sup>6</sup> used traditional methods of combining published data from different studies. Using the reported data from each study 2x2 tables were constructed that compared endometrial thickness measured at TVU versus 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%.

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.<sup>9</sup> Meta-analyses using individual patient data instead of published summary data have come to less optimistic, but more accurate conclusions. Individual patient data meta-analysis is even reported to be the “gold standard” for meta-analyzing randomized controlled trials.<sup>9-12</sup>

In diagnostic research the same might apply. Instead of combining reported accuracy measurements, individual patient data can be used to come to a more precise conclusion on diagnostic performance. With respect to TVU measurement of endometrial thickness, the exact endometrial thickness of each patient in each study can be used, instead of classification in a two-by-two table in which the endometrial thickness is classified above or below a particular cut-off level.

In this study we report an individual patient data meta-analysis on the diagnostic accuracy of endometrial thickness measurement in the detection of endometrial cancer in women with PMB. As there is little evidence regarding the preferred analytical strategy in analyzing individual patient data on diagnostic test accuracy, we used different statistical approaches to combine and summarize the individual patient data to explore whether different approaches also yield different results.

## Methods

### *Literature search, study selection*

We started our meta-analysis with three previous meta-analyses on this subject.<sup>6-8</sup> These meta-analyses were checked for included studies and after crosschecking duplicates were excluded.<sup>6-8</sup> In their meta-analysis, Tabor *et al.*<sup>7</sup> had already contacted individual authors with the request to supply data on mean and median endometrial thickness and 10th and 90th centiles. Those authors that had been unable to provide data for the meta-analysis Tabor *et al.*<sup>7</sup> were not contacted for the present IPD-meta-analysis, since we considered it highly unlikely that those authors that could not provide the required data to Tabor *et al.*<sup>7</sup>, would be able to provide us with their original data for the present meta-analysis. Furthermore, a MEDLINE search was performed identifying those studies reported since the published meta-analyses (2000-2006). Studies were included if they reported on women with PMB in whom endometrial thickness was measured by TVU. The outcome endometrial carcinoma had to be confirmed histologically. Histological specimens were collected using different methods. In more recent studies verification of diagnosis through histology sampling could have been omitted, since in these studies the established cut-off level for endometrial thickness may have been accepted and verification deemed unnecessary. If description of follow-up to verify outcome was sufficiently sought for all women recruited in the study, these studies were eligible for the meta-analysis.

### *Data gathering*

Contact information of the first and last authors was sought through MEDLINE (recent publications) or internet (e.g. google). The authors were then contacted through email, fax, conventional mail or telephone. In case contact information was not available or in case the first author did not respond, the last author was contacted. In a general invitation letter authors were explained about the concept of IPD meta-analysis. Initially, they were asked if they were interested to participate. In case they responded positively, they were asked to provide the original data for the analysis. The authors were asked to provide data on the absolute value of endometrial thickness, data on presence of endometrial cancer for each patient, and additional patient characteristics (age, time since menopause, HRT use, presence of diabetes,

hypertension, anticoagulants use and BMI). Authors could supply their data in any convenient format. If authors had new, original data available that were not included in the original publications, they were asked whether they were willing to share these data, on the condition that the data fulfilled the inclusion criteria of our study.

### ***Statistical analysis***

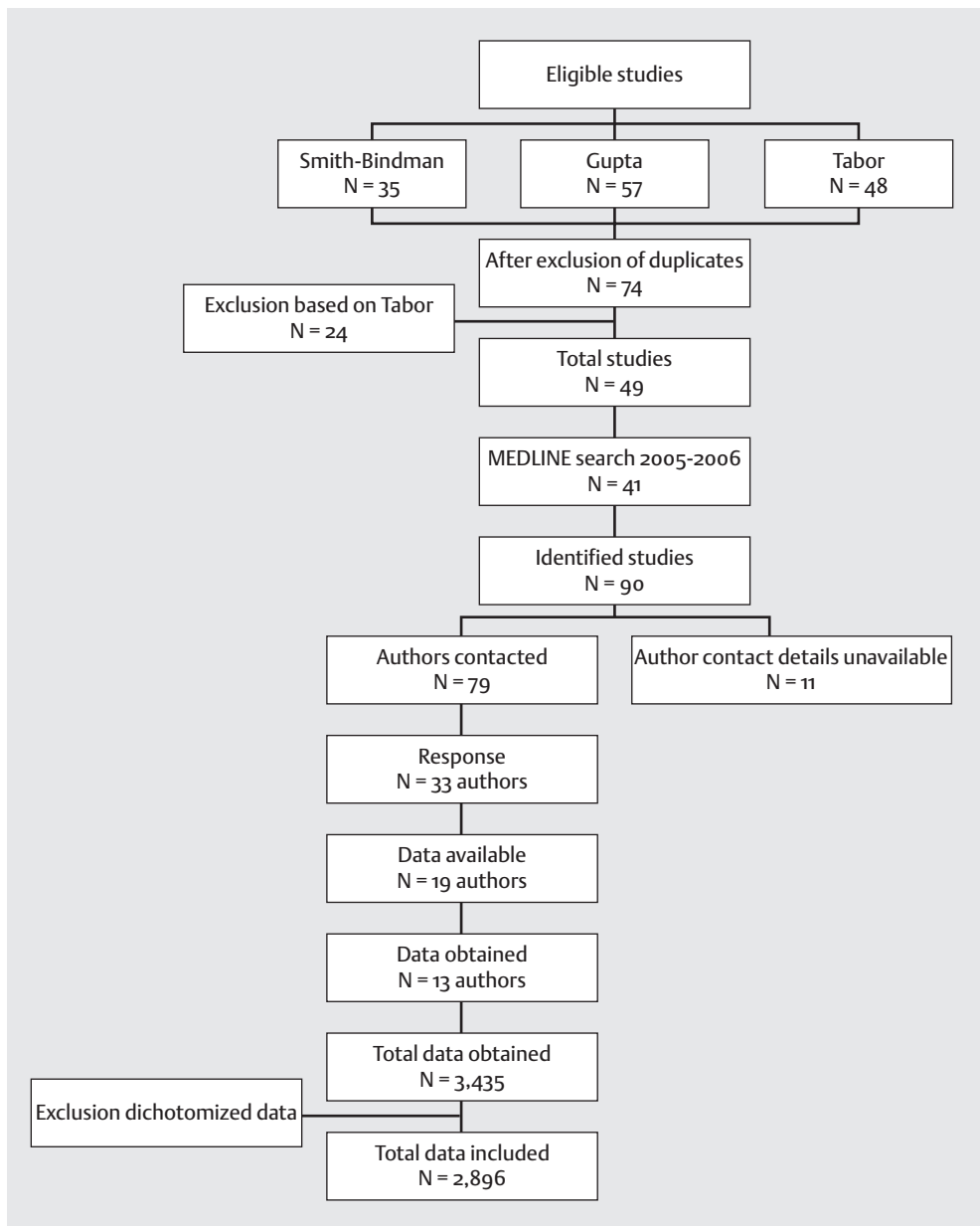
Distribution of endometrial thickness was calculated per study for patients with and patients without endometrial carcinoma separately. Subsequently, we applied different methods to determine diagnostic accuracy of endometrial thickness.

First, for each study a Receiver Operator Characteristics (ROC) analysis on endometrial thickness for endometrial carcinoma was performed and for each study an Area Under the Curve (AUC) was calculated. A mean AUC across studies was estimated, weighted for the sample size of each study. Second, data from all studies were pooled and directly analyzed for diagnostic accuracy: (1) ROC-analysis based on logistic regression irrespective of the original study; (2) ROC-analysis, in which we adjusted for differences in the distribution of endometrial thickness between studies in the pooled data by expressing endometrial thickness as multiples of the median (MoM) within each study; and (3) ROC-analysis based on a random effects logistic regression model, where the model allowed for different odds-ratios per study. The three ROC curves based on direct analyses of the individual patient data were then compared by plotting them in one graph, with the ROC curve based on the earlier reported conventional meta-analysis as a comparator.<sup>6</sup> Finally, a two stage approach was used, in which we introduced different cut-off levels for endometrial thickness per study of 1, 2, 3, 4, 5, 6, and 7 mm respectively. This meant that for a cut-off value of 4 mm, endometrial thickness > 4.0 mm was considered abnormal and endometrial thickness ≤ 4.0 mm was considered normal. For each cut-off level and for each study 2x2 tables were constructed, for which sensitivity and specificity were calculated. These sensitivities and specificities were analyzed simultaneously by using a non-linear random effects model to calculate summary estimates of sensitivity and specificity for a range of endometrial thickness cut-off levels. These summary estimates of sensitivity and 1-specificity were plotted along the other ROC curves.

## Results

A total of 90 publications were identified. Of 11 authors contact information was either not available or not correct. All remaining 79 authors were contacted, of which 33 authors replied and 13 authors provided their data (Figure 1).<sup>13-28</sup>

Figure 1. Flow chart of included studies





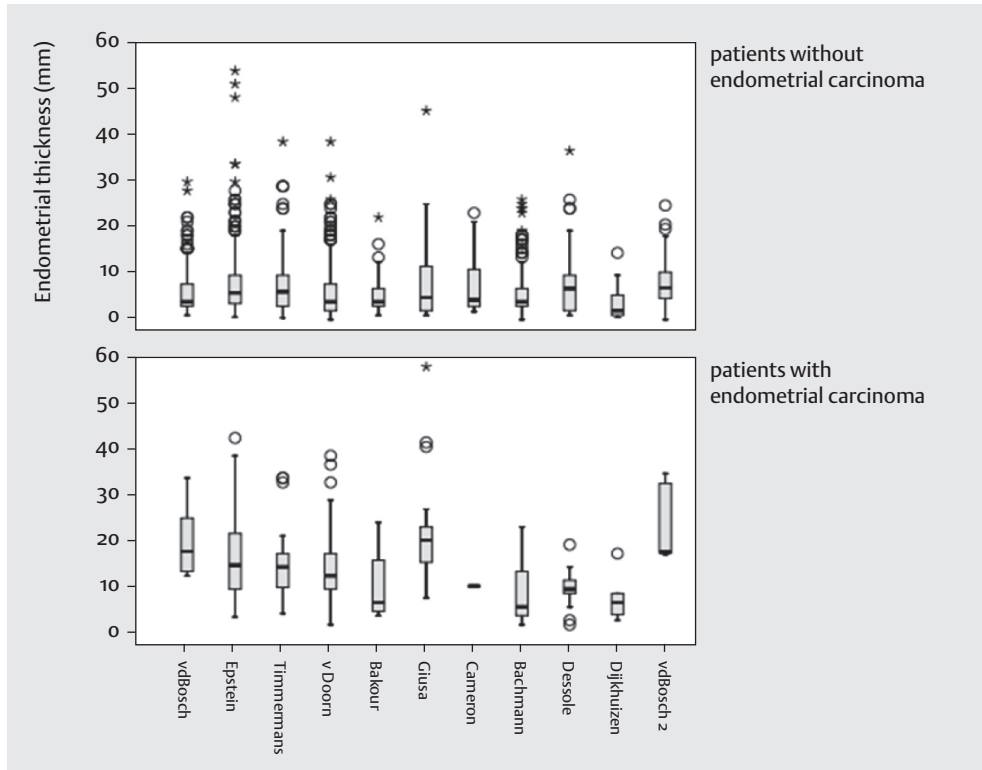
One author (Epstein) supplied data on several publications<sup>14-17</sup>; the data for these publications were gathered in one database containing consecutive patients during one study period; these data were considered to come from one study.<sup>14-17</sup> Another author (Van den Bosch) provided data from two publications<sup>13,28</sup>; the data for these publications were gathered in different hospitals in different time periods, therefore these data were not taken together, but considered to come from two studies.<sup>13,28</sup> Data on 3,435 patients, of which 296 had endometrial carcinoma, were available. Of two studies original endometrial thickness measurements had been dichotomized to endometrial thickness above or below 5 mm.<sup>21,27</sup> These studies were excluded in the present analysis, leaving data on 2,896 patients of which 259 had endometrial carcinoma. All other authors provided data on original endometrial thickness, age and diagnosis of endometrial carcinoma.<sup>13-20,22-26,28</sup> Table 1 presents information on different study characteristics, number of patients per study, prevalence of endometrial carcinoma, whether verification of diagnosis was complete or partial (through follow-up), study period and AUC of ROC-analysis. Figure 2 shows the range and median endometrial thickness in women with and women without endometrial carcinoma. The median endometrial thickness in patients without endometrial carcinoma varied from 2 to 7 mm between studies. The median endometrial thickness in patients with endometrial carcinoma varied more between the different studies (from 6 to 21 mm) (Figure 2).

**Table 1. Information on different included studies**

Author	No. of pts	No of EC (%)	Verification	Period	AUC (95% CI)
Vd Bosch	172	10 (5.8)	Complete	1993	0.93 (0.88-0.98)
Epstein	431	46(10.7)	Complete	1995-2001	0.83 (0.77-0.89)
Timmermans	426	29 (6.8)	Partial	2004-2007	0.83 (0.73-0.91)
V Doorn	913	94 (11.9)	Partial	2002-2003	0.87 (0.84-0.91)
Bakour	53	5 (9.4)	Complete	1996-1997	0.75 (0.53-0.96)
Cameron	40	1 (2.5)	Complete	2000	0.73 (0.58-0.89)
Giusa-Chiferi	80	19 (23)	Complete	1992-1995	0.87 (0.80-0.95)
Bachmann	385	25 (4.9)	Partial	1999-2001	0.68 (0.56-0.81)
Dessole	220	13 (4.5)	Complete	1999-2002	0.72 (0.58-0.85)
Dijkhuizen	77	11 (14.3)	Complete	1994	0.79 (0.68-0.90)
Vd Bosch	99	6 (6.1)	Complete	2003	0.97 (0.94-1.0)
<b>Total</b>	<b>2896</b>	<b>259 (8.9)</b>			<b>0.84</b>

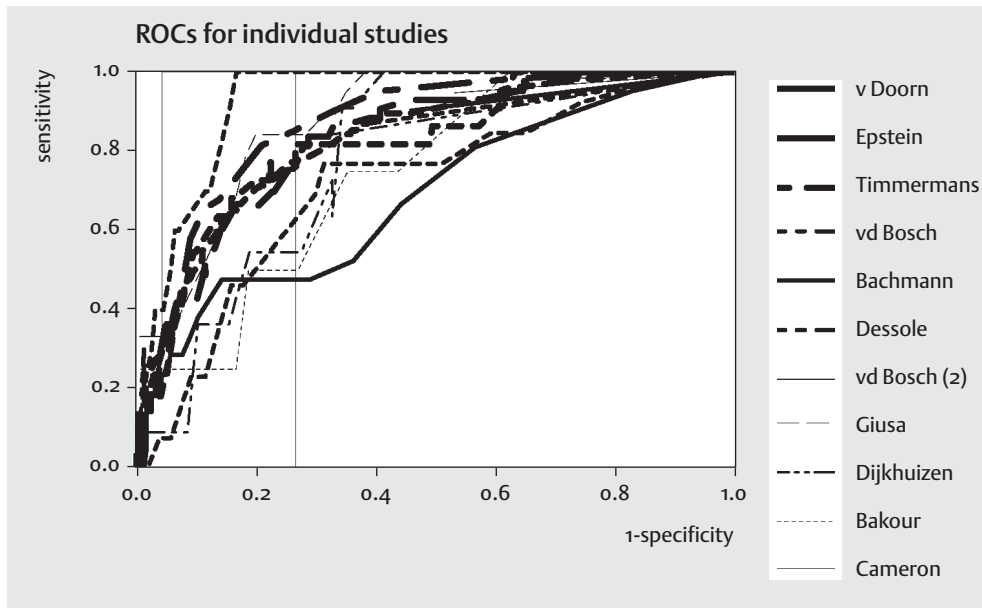
EC, endometrial carcinoma; AUC, Area Under the Curve (95% Confidence Intervals)

Figure 2. Distribution of endometrial thickness in patients with and patients without endometrial carcinoma per study



ROC analysis on endometrial thickness for endometrial carcinoma per study yielded AUCs between 0.68 and 0.93 (Table 1 and Figure 3). The mean AUC across studies weighted by the sample size of each study was 0.84. When data from all studies were pooled and analyzed irrespective of the original study, the ROC curve had an AUC of 0.82 (95% CI 0.80-0.85). When endometrial thickness was expressed as MoM per study, the AUC was 0.83 (95% CI 0.81-0.86), and the AUC based on the random effects logistic regression model was 0.84 (95% CI 0.82-0.87).

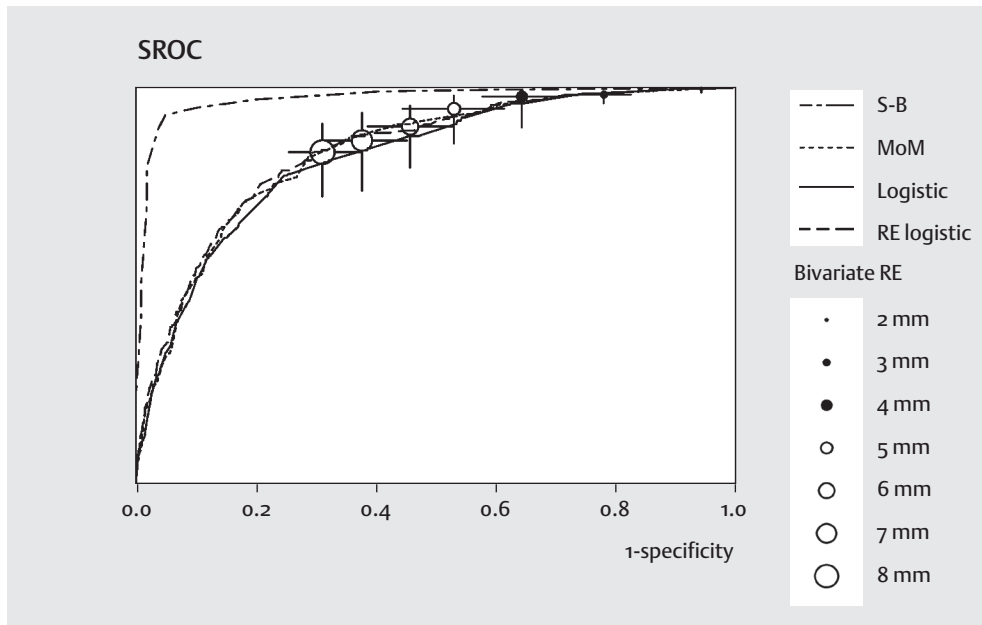
Figure 3. ROC-curves for each individual study (thickness of the lines represent sample size of each study)



Finally, for cut-off levels between 1 and 7 mm endometrial thickness, summary estimates based on the bivariate model decreased from 99.8 (95% CI 99.0 to 99.9) to 83.9 (95% CI 72.7 to 91.0) for sensitivity and increased from 5.4 (95% CI 3.1 to 9.1) to 68.7 (95% CI 62.4 to 74.3) for specificity. These estimates of sensitivity and 1-specificity were plotted as an ROC curve (Figure 4), and are located near the other ROC curves.

When these ROC curves were compared with the ROC of Smith-Bindman *et al.*<sup>6</sup> the overall diagnostic accuracy was lower (Figure 4). We looked at the commonly used different cut-off levels (4 mm and 5 mm).<sup>1,5,29</sup> In the present meta-analysis these were found to have a sensitivity of 94.8% (95% CI 86.1-98.2%) and a specificity of 46.7% (95% CI 38.3-55.2%) for 4 mm, and 90.3% (95% CI 80.0-95.5%) and 54.0% (95% CI 46.7-61.2%) for 5 mm respectively. A cut-off value of 3 mm was found to have a sensitivity of 97.9% (95% CI 90.1-99.6%) for a specificity of 35.4% (95% CI 29.3-41.9%).

Figure 4. Receiver Operator Characteristics Curve of endometrial thickness.



S-B: ROC curve of Smith-Bindman; MoM: ROC curve based on Multiples of the Median; Logistic: ROC curve based on logistic regression; RE logistic: ROC curve based on logistic regression with random-effects model; Bivariate RE: random-effects model combining different cut-off values (1-7 mm)

## Discussion

The present meta-analysis used individual patient data to estimate the diagnostic accuracy of endometrial thickness measurement by TVU for presence of endometrial carcinoma among women with PMB. Different methods of ROC analysis were used, which all resulted in comparable ROC curves. In all these analyses, we found that the diagnostic accuracy was lower than that of Smith-Bindman *et al.*<sup>6</sup> The commonly used cut-off value of 4 mm and 5 mm were found to have a sensitivity of 95% and 90% respectively. Only a cut-off value of 3 mm, yielded a high sensitivity of 98%.

The ROC curve is an informative way to present accuracy for each possible cut-off value of endometrial thickness measurement. For clinical practice, usually one cut-off value is used. The “optimal” cut-off value is determined by the consequences associated with false positive and false negative results. In the case of endometrial carcinoma, the consequences of false negative results are far stronger than the consequences of false positive results, i.e. one aims to exclude endometrial carcinoma with a high amount of certainty, and accepts therefore many

false positive diagnoses resulting in unnecessary endometrial biopsies. Therefore, clinicians aim for virtually 100% sensitivity.

A data-driven selection of optimal cut-off values is prone to bias. It potentially leads to overestimation of the sensitivity and specificity of the test under study. A data-driven approach to select the optimal cut-off value usually leads to a point above the true underlying ROC curve.<sup>30</sup> Consequently, combining these different reported cut-off values of smaller studies in a meta-analysis could lead to overestimation of diagnostic accuracy. The use of the original individual patient data can correct for this bias, as it ignores the reported optimal cut-off values, but incorporates the whole range of data. Moreover estimates are more precise because of increasing sample size.

Unfortunately, not all studies available on diagnostic accuracy of endometrial thickness could be included in the present meta-analysis. This was mainly due to the fact that authors did not have the original data available anymore. Since the mid 90's, in which the majority of the papers was published, many authors have moved and changed affiliation. Furthermore, information technology has rapidly changed leading to different computer programs and different ways of storing data. Although this lack of inclusion is a potential source of bias, we were able to report on 2,896 women across different studies. It seems likely that the lack of inclusion did not affect our results, since we were able to report on a high number of women. However, for future IPD research, solutions to solve this problem have to be explored. A possible solution could be that it becomes mandatory to supply journals with original databases once an article is published and that these databases are stored.

Apart from our meta-analysis there are three meta-analyses on this subject which have used different methods and have come to different conclusions.<sup>6-8</sup> Smith-Bindman *et al.*<sup>6,9</sup> performed a conventional meta-analysis using reported cut-off values, combining these in a summary ROC. Tabor *et al.*<sup>7</sup> used original data on endometrial thickness and 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%, implicating that a 10% pre-test probability would result in a post-test probability of 0.8%. Gupta *et al.*<sup>8</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. Pooling of the results of these four studies for endometrial thickness  $\leq 5$  mm resulted in a Likelihood Ratio (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%. Although Gupta *et al.*<sup>8</sup> and Tabor *et al.*<sup>7</sup> have come to less optimistic conclusions on the diagnostic accuracy of endometrial thickness measurement, the meta-analysis by Smith-Bindman *et al.*<sup>6</sup> has had the most impact on clinical practice. This meta-analysis is

mostly quoted in different guidelines and has the highest average citations per year in web of science (15.36 for Smith-Bindman *et al.*<sup>6</sup> compared to 5.29 for both Tabor *et al.*<sup>7</sup> and Gupta *et al.*<sup>8</sup>). The present IPD meta-analysis came to an overall lower diagnostic accuracy than the meta-analysis by Smith-Bindman *et al.*<sup>6</sup> When we looked at different cut-off values, a cut-off value of 3 mm (i.e. endometrial thickness > 3 mm warrants endometrial sampling) was found to have a high sensitivity of 98%. Cut-off values of 4 and 5 mm had a lower sensitivity than the previously reported 95% and 90% compared to 96% reported by Smith-Bindman *et al.*<sup>6</sup> This would argue for use of a 3 mm cut-off value.

To guide clinical decision making there is a need for good quality primary accuracy studies, of which the original data are retained so that they can eventually be included in subsequent IPD meta-analyses. Systematic reviews of test accuracy test have come available to summarize primary accuracy studies. However, there is ongoing debate about the most appropriate methodology for summarizing the available evidence in literature.

In conclusion, using individual patient data instead of reported data and optimal cut-off values of endometrial thickness measurement for endometrial carcinoma in women with PMB, leads to a less optimistic estimation of this diagnostic accuracy. Nonetheless, the a cut-off value of 3 mm has a sensitivity of 98%. Therefore, 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 PMB.

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