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Diagnostic delay of gynaecological cancer in women with postmenopausal bleeding

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ABSTRACT

INTRODUCTION. Postmenopausal bleeding is the primary reason for referral to the gynaecological fast-track suspected cancer programme due to an elevated risk of endometrial cancer. The aim of this study was to examine the diagnostic flow among women with postmenopausal bleeding.

METHODS. Data were collected and analysed from 362 women at Sygehus Sønderjylland referred with the International Classification of Diseases, tenth edition, diagnosis "DN950 postmenopausal bleeding" from 2015 to 2019.

RESULTS. We found a mean 83-day period between the initial consultation and the final cancer diagnosis. Combined, the 362 women underwent 354 diagnostic procedures of which 204 were endometrial sampling with aspiration (vabrasio). In 44% of the cases, sampling by vacuum aspirator was either unsuccessful due to pain or cervical stenosis or was deemed insufficient for pathological assessment. Gynaecological cancer was diagnosed in 16 (4%) of the women, hereof 13 (3.6%) had endometrial cancer.

CONCLUSIONS. We found a remarkable delay not complying with the intentions of national guidelines with respect to final diagnostics of endometrial cancer. Vacuum aspirator is a frequently used diagnostic tool, but has shortcomings in relation to the success rate of the procedure and insufficient sampling. Gynaecological cancer was found at a rate of 3-5% as reported by other Danish studies. Because of the limitations associated with a one-step diagnostic procedure with vabrasio, attention to follow-up may reduce diagnostic delay.

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TRIAL REGISTRATION. This study was registered with the Region of South Denmark (no. 21/18387) and Sygehus Sønderjylland (no. 1298-001) as a quality improvement project.

Postmenopausal bleeding (PMB) is a symptom that results in a referral to the fast-track cancer referral programme in Denmark due to an increased risk of endometrial cancer (EC). The programme recommends specialist evaluation within six days. If cancer is diagnosed, the recommendation is to initiate treatment within 29 days from referral [1]. A standard examination involves a transvaginal ultrasound and, in the case of an endometrium larger than 4 mm, an invasive procedure is performed such as vabrasio (endometrial sampling with vacuum suction by a syringe, e.g. pipelle or vaculok) or endometrial biopsy. Vabrasio is often used, among others, because it is immediately available in a one-step diagnostic procedure and is of a less invasive nature than cervical dilation and endometrial curettage [2].

PMB is the key symptom of EC in about 90% of the cases [3]. The one- and five-year risk of EC in Danish women with PMB is 5% [4]. The treatment of women with early-stage EC is hysterectomy and bilateral salpingo-oophorectomy with a favourable prognosis as the five-year survival rate is 84%, which is why early detection is

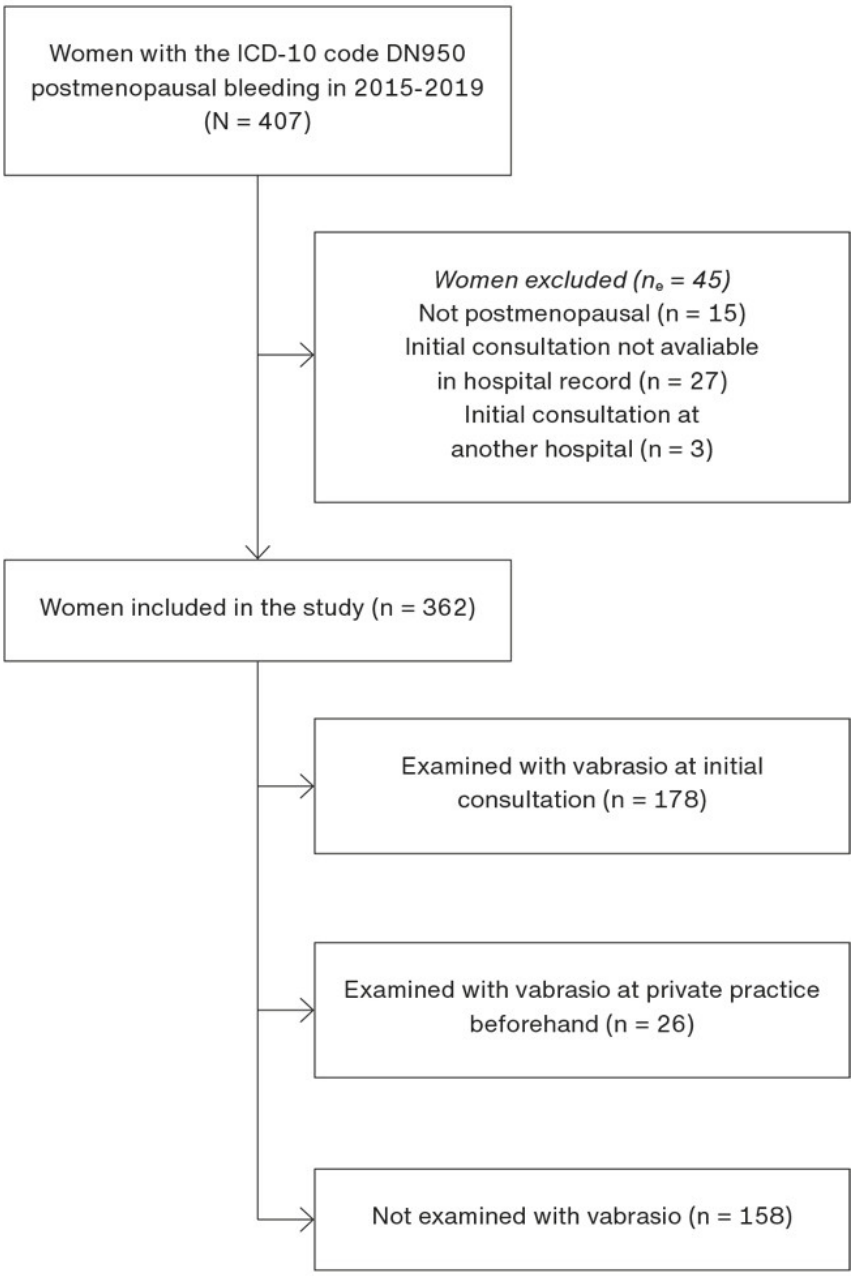
crucial [5].

The objective of this study was to examine the diagnostic flow among women with PMB at SygehusSønderjylland from 2015 to 2019 to determine if the practice in the gynaecological ward matches the intentions of the national guidelines regarding the diagnostics of symptoms of women who may have cancer.

METHODS

The electronic journal system Cosmic was used to identify women diagnosed with the International Classification of Diseases, tenth edition (ICD-10) code "DN950 postmenopausal bleeding" at the outpatient clinic at the Gynaecological Ward, Sygehus Sønderjylland – Aabenraa, Denmark, from 2015 to 2019. In total, 407 women were identified, 362 of whom were included. The 45 excluded women either had their initial consultation before 2015 or at another hospital, or they were not, in fact, postmenopausal (**Figure 1**). The registered data included date of birth, date of examination, type of examination, histological findings at first and subsequent examinations, height, weight, endometrial thickness and other relevant factors such as parity, hypertension, diabetes, polycystic ovaries, hereditary nonpolyposis colorectal cancer (HNPCC), current use of tamoxifen or hormone replacement therapy according to the prescription database (FMK). In cases of numerous examinations, the most abnormal histopathological results from the procedures were used. Data from private specialists were included if a relevant procedure had been performed less than one month from the initial visit at the hospital or if it formed part of the same diagnostic process. Thus, if the initial sampling was performed at a private specialist, the date when the histopathological results were received counted as time zero even before the woman showed up in the out-patient clinic. Diagnostic delay is from the first sampling at the private specialist or the initial date of visit in the out-patient clinic = time zero) to the date the endometrial malignancy was verified.

FIGURE 1 Inclusion, exclusion and initial vabrasio result.



ICD-10 = International Classification of Diseases, tenth edition.

For statistical analysis, we divided the women into three groups according to their initial sampling procedure. The three groups were vabrasio 1) at private practice, 2) at initial consultation and 3) not performed at first visit (Figure 1). We also sub-divided the women according to the result of their endometrial histology and to whether it was benign or malignant. For statistical calculations, IBM SPSS Statistics 28 was used. The difference between two means was tested with Student's t-test if data followed the Gaussian distribution; otherwise, the Mann-Whitney's test was used. The χ^2-test was used for categorical variables. Kaplan Meier analysis was used for evaluation of delay between the three initial sampling procedure groups. A two-sided $p < 0.05$ was the level of significance. Continuous values are given as mean ± standard deviation (SD) if a Gaussian distribution was found, otherwise as median (range).

Trial registration: Permission was granted as part of a quality improvement project on prevalence of EC by the Region of South Denmark (no. 21/18387) and Sygehus Sønderjylland (no. 1298-001).

RESULTS

The clinical data of the 362 women showed that women with subsequent malignant endometrium samples were older ($p < 0.002$) and that their BMI and age were slightly skewed, but the post-hoc testing did not reach significance for any single group with regard to the initial sampling procedure (**Table 1**). The women with no initial sampling were more likely nulliparous than those with an initial endometrial sampling ($p = 0.027$). No difference was seen in hypertension, diabetes, hormone replacement treatment, tamoxifen use, HNPCC or parity in the groups whether based on the initial sampling or on subsequent malignant endometrial results.

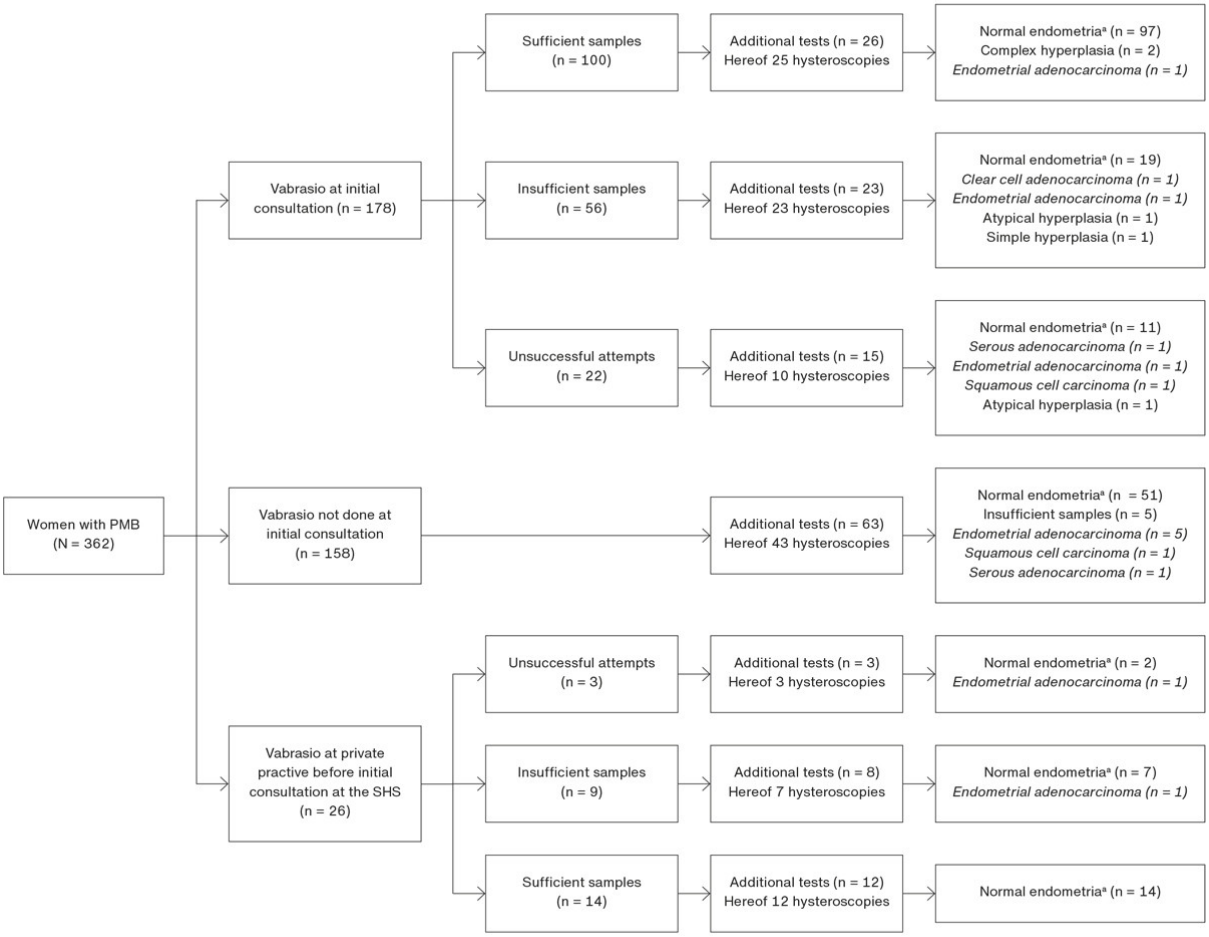
TABLE 1 Clinical data of 362 women with postmenopausal bleeding by initial vabrasio and subsequent endometrial malignancy.

	Vabrasio			Endometrial sample		
Kolonneheader	at private specialist ($n_p = 26$)	at initial visit in the outpatient clinic ($n_i = 178$)	not performed at the initial visit in outpatient clinic ($n_n = 158$)	benign ($n_b = 349$)	malignant ($n_m = 13$)	All women (N = 362)
Age, yrs, median (range)	64 (45-90)	62 (41-94)	66 (44-96)	63 (42-97)	77 (46-87)**	63 (41-97)*1
BMI, kg/m², median (range)[a]	29.3 (20-42)	28.5 (19-55)	25.4 (17-56)	27 (17-55)	28 (22-44)	27.1 (17-56)*1
Nulliparity, n (%)[b]	1 (4)	11 (6)	21 (13)	30 (9)	3 (23)	33 (11)*2
Hypertension, n (%)	13 (50)	79 (44)	70 (44)	153 (44)	9 (69)	162 (45)
Diabetes, n (%)	4 (15)	29 (16)	23 (15)	53 (15)	3 (23)	56(15)
HRT, n (%)	2 (8)	15 (8)	9 (6)	25 (7)	1 (7)	26 (7)
Tamoxifen treatment, n (%)	0	5 (3)	2 (1)	7 (2)	0	7 (2)
HNPCC, n (% of column)	0	0	1	1 (0.3)	0	1 (0.3)

*1) $p < 0.05$, ANOVA; *2) $p < 0.05$, Pearson χ^2-test; **) $p < 0.01$, Student's t-test.
ANOVA = analysis of variance; CI = confidence interval; HNPCC = hereditary non-polyposis colorectal cancer; HRT = hormone replacement therapy.
a) Data on BMI in 322 women.
b) Data on parity in 314 women.

In total, the 362 women with PMB underwent 354 diagnostic procedures, excluding Pap smears (**Figure 2**). Vabrasio accounted for 204 of these, among which 25 were unsuccessful samplings, 64 had insufficient material for pathological assessment and one sample went missing. In total, 90 (44%) of the 204 vabrasios failed to provide an endometrial diagnosis. Sampling was unsuccessful either due to cervical stenosis or because the women were unable to cooperate for the procedure. When considering only the 179 successful attempts of vabrasio, 35% of the samples had insufficient material for diagnosing. In 54% of the cases with insufficient or unsuccessful endometrial sampling, the women underwent a subsequent diagnostic procedure. Among the women with sufficient endometrial samples, 33% underwent a subsequent diagnostic procedure (Figure 2).

FIGURE 2 Flow chart of diagnostic procedures and final histological diagnoses.



PMB = postmenopausal bleeding; SHS = Sygehus Sønderjylland.
a) Benign pathology in the endometrial sampling, including polyp, leiomyoma, atrophy and non-complex hyperplasia.

Hysteroscopy was applied in 123 women after their initial visit, hereof 43 in 158 women who had no vabrasio at their first visit, 22 in 26 women in whom vabrasio was performed in private practice and 58 in 178 women in for whom vabrasio was performed in our outpatient clinic. The EC incidence was 7% (3/43), 5% (1/22) and 7% (4/58) in these three hysteroscopy groups, respectively (Figure 2). Five cases of EC had no hysteroscopy: One was diagnosed with vabrasio at the initial sampling in our clinic, two were diagnosed with vabrasio at the second visit after no sampling had been performed at the first visit, one after repeated vabrasio from private practice where the initial sampling revealed insufficient material, and one after repeated vabrasio where the first vabrasio showed complex hyperplasia. In summary, all ECs were diagnosed at the initial vabrasio (n = 1), by repeated vabrasio (n = 4) and by hysteroscopy at the second visit (n = 8). Fifty-one of the hysteroscopies were performed in the outpatient department with use of local anaesthetics, whereas 72 were performed under general anaesthesia. EC was subsequently diagnosed in two (4%) and six (8%) of the hysteroscopies.

We defined postmenopausal as one year of amenorrhoea in our inclusion criterion (Figure 1). Furthermore, the diagnosis was used that stated on the referral triggering the fast-track referral programme. A review of the data showed that 60% of the women were > 60 years and 80% were > 55 years. In total, 18 (5%) women were below 50 years; among these women, one was diagnosed with an EC and six showed atrophia/inactive endometrium. Further, one woman was treated with hormone replacement therapy (HRT) and showed a proliferative endometrium at sampling.

Among the women with PMB, 207 (57%) underwent successful endometrial sampling. The most common

histological diagnoses were polyp (35%), endometrium (33%), atrophy (10%), leiomyoma (8%) and non-complex hyperplasia (6%). A total of 16 women (4%) were diagnosed with a gynaecological cancer. Among these cancers, 13 were EC (4%), two were cervical cancer (0.6%) and one was ovarian cancer (0.3%). The women who were diagnosed with EC were older than those without malignancies ($p < 0.01$, Table 1). Among the 16 women with malignant histopathology samples, one was diagnosed from a procedure performed during the initial consultation, six from a single procedure performed later in the process and nine received their diagnosis after multiple diagnostic procedures. As part of the diagnostic work-up, nine of the 16 women were examined with a vabrasio. Among these nine samples, four were unsuccessful, three had insufficient material, one showed complex hyperplasia and one showed endometrial adenocarcinoma.

We found a mean 83-day period from initial consultation to the final diagnosis of cancer in the 16 women. The delay was not associated with whether initial sampling was performed or not or whether the sampling was performed at the outpatient clinic or at a private specialist ($p = 0.5$, Kaplan-Meier). Considerable variation was seen in terms of days before diagnosis (median 51 days (range: 0-299 days)). The two women with the longest delay to the final diagnosis waited for 299 and 261 days, respectively. They did not attend their follow-up appointment, and the department did not pursue the case further despite having no endometrial sample from the initial consultation. They were subsequently re-referred with continuous PMB and the cancer diagnosis was confirmed. Five of the 16 women who eventually received a cancer diagnosis did not have a diagnostic procedure performed during their initial consultation; three due to pain and non-cooperation and two due to cervical stenosis. Three of the 16 women underwent an initial diagnostic procedure but had benign pathology in this sample. In these cases, EC was found at a subsequent follow-up. In two of the 16 cases, the diagnostic procedure was delayed due to the need for cardiac evaluation before anaesthesia.

DISCUSSION

We found considerable variation in the flow of women with PMB after the referral to the supposedly fast-track suspected cancer programme. For women with a subsequent cancer diagnosis, an average 83 days passed from the first visit to ascertainment of malignancy and most of the women underwent several diagnostic procedures before receiving their final diagnosis. The intentions in the national guidelines and the fast-track cancer referral programme are to ensure and increase the quality of care, eliminate unnecessary delay and enable transparency about the patients' potential diagnosis. Furthermore, the recommendation specifies that the diagnostic process should be performed within 15 days and that initial treatment should be initiated within 29 days from the referral [1]. However, this is a general recommendation - not a patient right. Given individual circumstances and considerations, the process may therefore be extended. Thus, the examined delay reveals a disparity between reality and the national guideline recommendations. Scrutinising each individual case showed that different circumstances caused the delay as some displayed non-cooperative behaviour, comorbidity and an initially benign pathology. Even though these circumstances are, to some extent, understandable, the observed delay still much exceeded recommendations. A nationwide Danish study on gynaecological cancer found these conditions to be ubiquitous in the flow of patients [6]. Furthermore, the women with EC experienced a median of 61 days of secondary care delay, i.e. time from referral from their general practitioner to surgery, 10% even had a secondary care delay of 138 days or longer. Thus, we found that the median initial diagnostic delay was twice that recommended. Even though this does not include secondary care delay, the degrees of delay were comparable. Our study findings in this respect are similar to the national level median delay and far from the recommendations in terms of waiting time [6].

The delay in the patient flow among women with PMB may lead to considerations relating to the diagnostic methodology applied. Vabrasio is popular owing to its immediate availability as a one-step diagnostics

procedure. However, the procedure was either unsuccessful or had insufficient material for pathological assessment in almost half of the women in this study. A similar Danish study by Andersen et al. reported that 17% of vabrasios had insufficient material and 0.2% procedure attempts were unsuccessful [7], which is considerably lower than our findings. The study by Andersen et al. examined women identified with the procedure ICD-10 code for vabrasio and not by their referral diagnosis, so its conclusion characterises the efficiency of the procedure and not of the fast-track programme on PMB.

Another point may be that unsuccessful attempts were missed at an undisclosed rate, probably because they were not coded as such. Thus, the results are not an evaluation of diagnostic strategies in PMB. Our high incidence of insufficient samples may be due to changes in the criteria determining what is sufficient for histopathological specimens either locally or over time. A study by Adambekov et al. on pipelle sampling found a 23% failure rate in procedures; hereof 17% that were due to inability to access the endometrium and 80% to inadequate sampling. PMB as an indication for biopsy and age above 55 years was associated with pipelle biopsy sampling failure [8]. This may serve, in part, to explain the high failure rate of endometrial sampling in our study since all the included women were postmenopausal and most were above 55 years old.

Furthermore, comorbidity was present in a large proportion of the included women with 45% having hypertension and 15% diabetes. Vabrasio is less invasive than other diagnostic procedures such a dilation and curettage, which often require general anaesthesia. Vabrasio, therefore, saves women from more extensive procedures and from unnecessary anaesthesia in a considerable number of cases. However, our study suggests that more attention to follow-up may be appropriate in patients with PMB. Thus, despite the limitations related to achieving adequate sampling, vabrasio is a sensible choice as part of the initial diagnosing owing to its potential as a one-step diagnostic procedure and because it is less invasive than other relevant procedures. The flow on unsuccessful and not performed sampling in PMB women may potentially be assessed in an algorithm with criteria that should alert the physician to repeat diagnostic efforts.

CONCLUSIONS

We found a remarkable delay in the flow of women referred within a fast-track suspected cancer programme due to PMB. Gynaecological cancer was found at a rate of 3-5% as also reported by other Danish studies [4, 7, 9]. Furthermore, we found that due to the limitations of a one-step diagnostic procedure with vabrasio, attention to follow-up may lead to shorter diagnostic delays.

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REFERENCES

1. Danish Health Authority. Pakkeforløb for kræft i livmoderen, 2019. https://www.sst.dk/da/udgivelser/2019/pakkeforloeb-for-kraeft-i-livmoderen (28 Sep 2021).
2. Behnamfar F, Arshad E. Diagnostic values of pipelle and standard curettage compared to hysterectomy pathology in postmenopausal bleeding: a comparative study. Adv Biomed Res. 2020;9:58.
3. Clarke M, Long B, Del Mar Morillo A et al. Association of endometrial cancer risk with postmenopausal bleeding in women: a systematic review and meta-analysis. JAMA Intern Med. 2018;178(9):1210-22.

4. Bengtsen M, Veres K, Nørgaard M. First-time postmenopausal bleeding as a clinical marker of long-term cancer risk: a Danish nationwide cohort study. Br J Cancer. 2020;122(3):445-51.
5. Braun MM, Overbeek-Wager EA, Grumbo RJ. Diagnosis and management of endometrial cancer. Am Fam Physician. 2016;93(6):468-74.
6. Robinson K, Ottesen B, Christensen K, Krasnik A. Diagnostic delay experienced among gynecological cancer patients: a nationwide survey in Denmark. Acta Obstet Gynecol Scand. 2009;88(6):685-92.
7. Andersen A, Lauszus FF. Vabrasio is a reliable test to rule out endometrial cancer. Dan Med J. 2015 62(8):A5124.
8. Adambekov S, Goughnour SL, Mansuria S et al. Patient and provider factors associated with endometrial Pipelle sampling failure. Gynecol Oncol. 2017;144(2):324-8.
9. Dueholm M, Hjorth I, Dahl K et al. Ultrasound scoring of endometrial pattern for fast-track identification or exclusion of endometrial cancer in women with postmenopausal bleeding. J Minim Invasive Gynecol. 2019 26(3):516-25.