Risk assessment of endometrial cancer and endometrial intraepithelial neoplasia in women with abnormal bleeding and implications for clinical management algorithms

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Abstract

Background: Most endometrial cancer cases are preceded by abnormal uterine bleeding, offering a potential opportunity for early detection and cure of endometrial cancer. While clinical guidelines exist for diagnostic workup of abnormal uterine bleeding, consensus is lacking regarding optimal management for women with abnormal bleeding to diagnose endometrial cancer.

Objective: We report the baseline data from a prospective clinical cohort study of women referred for endometrial evaluation at the Mayo Clinic, designed to evaluate risk stratification in women at increased risk for endometrial cancer. Here, we introduce a risk-based approach to evaluate diagnostic tests and clinical management algorithms in a population of women with abnormal bleeding undergoing endometrial evaluation at the Mayo Clinic.

Study Design: A total of 1,163 women aged 45 years were enrolled from February 2013-May 2019. We evaluated baseline absolute risks and 95% confidence intervals of endometrial cancer and endometrial intraepithelial neoplasia according to clinical algorithms for diagnostic workup of

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women with postmenopausal bleeding (assessment of initial vs. recurrent bleeding episode and endometrial thickness measured via transvaginal ultrasound). We also evaluated risks among women with postmenopausal bleeding according to baseline age (<60 vs. 60+ years) as an alternative example. For this approach, biopsy would be conducted for all women aged 60+ years and those aged <60 years with an endometrial thickness of >4mm. We assessed the clinical efficiency of each strategy by estimating the percent of women who would be referred for endometrial biopsy, the percent of cases detected and missed, and the ratio of biopsies per case detected.

Results: Among the 593 women with postmenopausal bleeding, 18 (3.0%) had endometrial intraepithelial neoplasia and 47 (7.9%) had endometrial cancer and among the 570 premenopausal women with abnormal bleeding, 8 (1.4%) had endometrial intraepithelial neoplasia and 7 (1.2%) had EC. Risks were highest in women aged 60+ years 17.7% (13.0–22.3%), followed by those with recurrent bleeding (14.7%, 11.0–18.3%). Among women with an initial bleeding episode in whom transvaginal ultrasound is recommended, endometrial thickness did not provide meaningful risk stratification: risks of endometrial cancer/endometrial intraepithelial neoplasia were nearly identical in women with an endometrial thickness of >4mm (5.8%; 1.3–10.3%) and 4mm (3.6%; 0.9–8.6%). In contrast, among those aged <60 years with an endometrial thickness of >4mm, the risk of endometrial cancer/endometrial intraepithelial neoplasia was 8.4% (4.3–12.5%) and in those with an endometrial thickness of 4mm, the risk was 0% (0.0–3.0%; p=0.010). The most efficient strategy was to perform biopsy in all women aged 60+ years and among those aged <60 years with an endometrial thickness of >4mm, with the lowest percentage referred to biopsy while still detecting all cases.

Conclusions: Current clinical recommendations for endometrial cancer detection in women with abnormal bleeding are not consistent with underlying risk. Endometrial cancer risk factors such as age can provide important risk stratification compared to the assessment of recurrent bleeding. Future research will include a formal assessment of clinical and epidemiologic risk prediction models in our study population as well as validation of our findings in other populations.

Condensation:

A risk-based approach to evaluating diagnostic testing for endometrial cancer in women with abnormal bleeding suggests that practice recommendations may not reflect underlying risk.

Keywords

Endometrial cancer; endometrial intraepithelial neoplasia; abnormal bleeding; postmenopausal bleeding; transvaginal ultrasound; endometrial biopsy; risk assessment

Introduction

Endometrial cancer (EC) incidence and mortality rates have increased over the past decade[1, 2], with 61,880 cases and 12,160 deaths occurring in the U.S. in 2019.[3] Approximately 80% of ECs present with stage I disease, with high 5-year survival. In contrast, 5-year survival for stage III and stage IV cancers is 69% and 16%, respectively, underscoring the promise of early detection.[4–6] Approximately 90% of EC cases are

preceded by abnormal uterine bleeding in premenopausal or perimenopausal women (AUB) or postmenopausal bleeding (PMB), offering a potential opportunity to detect and cure ECs that are destined to metastasize with delayed diagnosis..[7, 8] However, abnormal bleeding is a common symptom of many benign diseases, and only indicates the presence of EC in approximately 9% of postmenopausal women and 1–2% of premenopausal women[7, 9], suggesting that many women at low-risk undergo unnecessary invasive diagnostic procedures to rule out cancer.

In the U.S., methods for endometrial evaluation include transvaginal ultrasound (TVUS) and endometrial sampling, with or without hysteroscopy[10–12]; however, there is no consensus regarding the optimal sequence or combination of these procedures.[8] Absolute risk estimates are important for guiding clinical management and for evaluating new biomarkers and risk prediction tools as they are developed[13]; however, they have not been systematically evaluated in clinical populations.

We designed a prospective clinical cohort study to evaluate endometrial cancer risk prediction approaches among women with abnormal bleeding undergoing diagnostic evaluation at the Mayo Clinic. We present a baseline analysis evaluating a risk-based approach to clinical management algorithms in this population.

Materials and Methods

Study Population

We conducted a cross-sectional analysis of baseline data from our prospective clinical cohort study of women undergoing endometrial evaluation at the Mayo Clinic.[14] Women presenting to the Mayo Clinic's Department of Obstetrics and Gynecology were prospectively enrolled from February 21, 2013 through May 21, 2019 with passive follow-up via electronic medical record abstraction every 6 to 12 months. The current analysis includes data from the enrollment visit only. Eligible women included those 45 years with pre- or perimenopausal AUB or PMB. AUB was defined by symptoms of heavy menstrual bleeding, intermenstrual bleeding, menometrorrhagia, irregular menses, or other AUB among women aged 45 years who were not in menopause. Exclusion criteria included prior hysterectomy, prior pelvic radiation, endometrial sampling within the past 3 months, current pregnancy, and inadequate endometrial sampling. This study was approved by the Mayo Clinic and National Cancer Institute Institutional Review Boards; written informed consent was obtained from all participants prior to study enrollment.

Clinical Evaluation

Women underwent clinical evaluation of the endometrium as determined by their care provider. Clinical testing included any combination of the following: TVUS, office hysteroscopy, and office endometrial biopsy. If complete workup in the clinic was not feasible, women underwent assessment under anesthesia via hysteroscopy and dilation and curettage. Hysterectomy was performed if clinically indicated.

Transvaginal Ultrasound.—TVUS was performed as clinically indicated and interpreted by radiologists specialized in pelvic ultrasound. Endometrial stripe thickness (ET) was reported in millimeters (mm).

Hysteroscopy.—Office hysteroscopy using a flexible 3.1 mm diagnostic scope was performed per the clinician's discretion taking into account patient age, imaging findings, and clinical feasibility.

Endometrial Sampling.—All women enrolled in this study were anticipated to undergo diagnostic evaluation via endometrial sampling. This was performed as a clinic endometrial biopsy with a Pipelle (Pipelle® CooperSurgical, Turnbull, CT) or Endosampler device (MedGyn, Addison, IL) or as a D&C if clinic biopsy was not feasible. Pathology diagnoses were made clinically by gynecologic pathologists.

Outcome Definitions

Among women who did not require a hysterectomy, the final pathology diagnosis of endometrial biopsy or curettage was considered the reference diagnosis. Among women who underwent hysterectomy, the most severe pathology diagnosis on either the endometrial sampling or hysterectomy specimen was considered the final study diagnosis. Women deemed not to require endometrial biopsy were included in the benign group (N=110). Of these, 105 (95.5%) were confirmed to be at very low risk based on being premenopausal (42.7%) or having PMB with an ET of 4mm and/or a benign finding on hysteroscopy (52.7%). Removal of the remaining 5 women from risk estimate calculations did not change the results in a sensitivity analysis (not shown).

Final endometrial pathology diagnoses from the baseline visit were classified as: Benign, including women with a normal endometrium, endometrial polyps, disordered proliferative endometrium (DPEM), endometrial hyperplasia without atypia, or other benign histologic findings (e.g., endometritis, fibroids); endometrial intraepithelial neoplasia (EIN), including all diagnoses of hyperplasia with atypia, and EC.

Endometrial Cancer Risk Factors and Clinical Characteristics

Information on clinical risk factors for EC including the indication for endometrial sampling, bleeding type, age, race and ethnicity, body mass index (BMI; categorized as underweight or normal weight (<25 kg/m^2), overweight (25 to <30 kg/m^2) and obese (30 kg/m^2))[15], hypertension, type II diabetes, and smoking history were abstracted from electronic medical records. Other epidemiologic risk factors including tamoxifen exposure, current hormone use (combined progestin and estrogen formulations), past oral contraception (OC) use, and parity were ascertained via patient interview. Among postmenopausal women, PMB was characterized as either initial episode of bleeding or recurrent bleeding (any occurrence of bleeding after prior evaluation for PMB).

Clinical Algorithms for Evaluating Women with PMB and AUB

We used the current guidelines from the American College of Obstetricians and Gynecologists (ACOG) which recommend either endometrial sampling or TVUS for

evaluation of women with an initial episode of PMB. If TVUS is performed and the resulting ET measurement is 4mm, endometrial sampling is not required. In women with an ET >4mm, endometrial tissue sampling is recommended. Among women with recurrent PMB, endometrial sampling is recommended regardless of ET.[11, 12] For pre- or perimenopausal women with AUB who are 45 years, endometrial sampling is recommended as a first-line test.[10] In this study, diagnostic evaluations were not performed in the exact sequence as recommended by ACOG, but we simulated the sequential diagnostic process.

Statistical Analysis

We calculated absolute risks of detection at baseline (i.e. prevalent risk) of EC, EIN, and benign outcomes by select baseline characteristics, separately by menopausal status. Absolute risks were compared across baseline characteristics using Chi-square tests. Given that hysterectomy is standard of care for both EIN and EC, we evaluated combined baseline risks (EC/EIN) according to clinical algorithms for diagnostic workup of women with PMB and AUB. For women with PMB, risks were calculated as the proportion of women diagnosed with EC or EIN among all women in sequential strata defined as: bleeding pattern (initial or recurrent) and ET (4mm and >4mm). For women with AUB, we calculated the baseline risk of EC or EIN in all women. To illustrate how our analysis can be used to evaluate strategies for risk assessment, we calculated risks among women with PMB dichotomizing baseline age as <60 years vs. 60 years (determined a priori based on the average age of women diagnosed with endometrial cancer)[16], as an alternative to the assessment of recurrent bleeding. We plotted the risk estimates for each strategy, with marker size weighted by the corresponding number of women in each stratum. For all analyses, we also separately evaluated risks for EC only and among women not currently using hormones. For each analysis, we compared absolute risk estimates using t-tests.

We evaluated the clinical efficiency of each strategy by estimating the percent of women referred for endometrial biopsy, the percent of EC/EIN detected and missed, and the number of biopsies required to detect an EC/EIN. All analyses were performed in Stata 15 and R 3.5.3. Statistical tests were two-sided with $p < 0.05$ considered significant.

Results

In total, 2,782 eligible patients presented for EC evaluation at Mayo Clinic between February 2013 and May 2019. Of 1,460 women enrolled and consented, 1,163 women met inclusion criteria of being 45 years or older (mean 54.6 years) with either PMB or AUB (Figure 1).

Baseline Characteristics and Risk of Worst Outcome Among Women with PMB and AUB

Among 593 women with PMB, 528 (89.0%) had a benign diagnosis, 18 had EIN, and 47 were diagnosed with EC (absolute risks of 3.0% and 7.9%, respectively) (Table 1). Absolute risks of EC were highest in women 60 years (14.6%; p-value<0.0001), in those not currently using hormones (10.1%; p-value=0.002), obese women (9.8%; p-value <0.0001), and women with type II diabetes (21.6%; p-value<0.0001). Women with recurrent PMB had

higher risks of EIN and EC (4.5% and 10.1%, respectively) compared to those with an initial episode (0.5% and 5.1%, respectively; p-value=0.002). Among women with PMB and available ET measurements (n=430, 72.5%), the risks of EIN and EC were significantly higher in women with an ET of >4mm (4.2% and 10.1%, respectively) compared to those with 4mm (0% and 1.6%, respectively; p-value=0.001) (Table 1).

Among 570 premenopausal women with AUB, 555 had a benign diagnosis (97.4%), 8 had EIN and 7 had EC, corresponding to risks of 1.4% and 1.2%, respectively. Nulliparity was associated with a statistically significant increased risk of EC (p-value=0.035; Table 1).

Evaluation of Management Algorithms for PMB

We evaluated risks of EC/EIN following a sequential diagnostic process according to ACOG guidelines[11]. Absolute risk estimates for EC/EIN are shown in Figure 2. Among women with PMB, the risk in those with recurrent bleeding was 14.7% (95% CI=11.0–18.3%) compared to 5.6% (95% CI=2.5–8.6%) in women with an initial bleeding episode (p=0.0008). Among women with an initial bleeding episode, when TVUS is recommended as a first line evaluation, ET did not provide meaningful risk stratification: risks of EC/EIN were not significantly different in women with an ET of >4mm (5.8%; 95% CI=1.3–10.3%) versus those with an ET of 4mm (3.6%; 95% CI=0.9–8.6%). In contrast to those with an initial bleeding episode, TVUS provided additional risk stratification among women with recurrent bleeding such that women with an ET >4mm had the highest risk of EC/EIN (19.4%; 95% CI=13.8–25.0%) while in women with an ET of 4mm the risk was 0.0% (95% CI=0.0–6.0%; p=0.0001). In women presenting with recurrent bleeding and no ET measurement, the risk was 15.2% (95% CI=8.1–22.2%). We observed similar results for risk of EC alone (Supplemental Figure 1). Risks among women not currently using hormones were generally higher, although risk patterns were similar (Supplemental Figure 2).

As an alternative to the current clinical recommendation, we evaluated using age (<60 and 60 years) instead of recurrent bleeding as the first risk stratifier (Figure 3). Among women aged 60 years, the risk of EC/EIN was 17.7% (95% CI=13.0–22.3%) compared to 5.9% (95% CI=3.4–8.4%) in women aged <60 years (p<0.0001). In those aged <60 years with an ET of >4mm, the risk of EC/EIN was 8.4% (95% CI=4.3–12.5%) and in those with an ET of 4mm, the risk was 0% (95% CI=0.0–3.0%; p=0.010). Among women aged 60 years with an ET >4mm the risk of EC/ EIN was 22.3% (95% CI=15.2–29.5%), compared to a risk of 4.2% (95% CI=1.2–14.0%) in those with an ET of 4mm (p=0.005). We observed similar results for risk of EC alone (Supplemental Figure 3). Risks among women not currently using hormones were generally higher, although risk patterns were similar (Supplemental Figure 4).

Clinical Efficiency of Algorithms for Diagnostic Evaluation of PMB and AUB

We evaluated implications of different clinical algorithms on detection of EC/EIN and number of biopsies performed among all women. First, we evaluated existing clinical recommendations for women with PMB[11]: When referring all women with PMB to biopsy, all women would undergo biopsy, with 100% of EC/EIN cases detected at a ratio of 9.7 biopsies per case (Table 2). In the second recommendation of referring all women with

recurrent PMB as well as those with initial PMB and ET >4mm to biopsy, 87% of women would receive a biopsy with 97% disease detection at a ratio of 6.7 biopsies per case. In a third scenario that is currently not within ACOG recommendations, when referring all women aged 60 years and those aged <60 years with an ET of >4mm to biopsy, referral would be lowest (82%) with 100% disease detection at a ratio of 5.9 biopsies per case. Among premenopausal women aged 45 years with AUB, endometrial sampling is the only ACOG recommendation.[10] All women would undergo biopsy with 100% of EC/EIN detected at a ratio of 38 biopsies per case.

Comment

Principal Findings

We applied a risk-based approach to evaluate diagnostic tests and recommended clinical management algorithms[10, 11] to inform decision-making in women with abnormal bleeding. We demonstrate that current diagnostic strategies are not consistent with underlying risk of EC/EIN. For example, TVUS is recommended as a first line test in women with PMB, with biopsy indicated for those with an ET of >4mm.[11] However, in our study, women had nearly the same risk of EC/EIN irrespective of ET. In contrast, among women with recurrent bleeding, TVUS provided good risk stratification such that those with a thickness of >4mm had a 1 in 5 risk of EC/EIN while no cases were found in women with a thickness of 4mm. To illustrate the principle of risk-based management, we evaluated an alternative approach using age with a cutoff of 60 years followed by TVUS. Among women with PMB aged <60 years, TVUS provided better risk stratification such that women with a thickness of 4mm would be safely reassured of 0% EC/EIN risk, while those with a thickness of >4mm had an 8% risk. Women aged 60 years with PMB had a EC/EIN risk of 17.7% that was similar to the risk among women with recurrent bleeding and an ET measurement of >4mm (19.4%).

Results in the Context of What is Known

Current guidelines recommend considering clinical risk factors such as age, obesity, and use of unopposed estrogen when evaluating PMB[12]; however, guidance lacks on how to integrate these factors for clinical-decision making. In our study, using age yielded better risk stratification compared to other clinical risk factors such as BMI; age is a highly reliable risk factor that is easily ascertained. While type II diabetes was associated with a very high absolute risk of EC, the prevalence of type II diabetes was low in our study, and most cancers occurred among women without type II diabetes. Risks among women not currently using hormones were higher compared to hormone users, consistent with the protective effects of combined estrogen/progestin formulations on the endometrium.[17] Irregular uterine bleeding is also a common side effect of hormone therapy; therefore, PMB is more frequently secondary to hormone therapy, rather than a symptom of EC/EIN.[7] Few clinical risk prediction models have been developed that combine multiple epidemiological and clinical risk factors.[18–20] However, these models have not been evaluated in target populations. Currently, there are no established absolute risk thresholds that guide clinical management. Our study shows a path towards developing risk-based management of women with abnormal uterine bleeding.

Clinical Implications

The growing clinical burden of EC, and the possibility to improve survival with early detection, highlight the importance of management guidelines for women with PMB and AUB. Differences in approaches can make it difficult to evaluate the clinical performance of current diagnostic strategies for EC and new tests that are being developed. We assessed the clinical efficiency of these strategies by estimating the percentage of women who would undergo endometrial biopsy, sensitivity of disease detection, and the ratio of biopsies performed to cases detected. In our population, risk assessment including age was most efficient, with the lowest percentage referred to biopsy while still detecting all cases. Results from our analysis emphasize the clinical challenge of managing premenopausal women with AUB, who have very low risks of EC/EIN.[9] Current guidelines recommend endometrial biopsy for premenopausal women aged 45 years with AUB.[10] Only 7 EC and 8 EIN were diagnosed in pre- and perimenopausal women with AUB, corresponding to 2.6% risk of EC/EIN combined, respectively. The efficiency of disease detection was much lower in these women, requiring 38 biopsies per case compared to 5.9–9.7 for strategies in women with PMB. Importantly, we did not observe strong risk stratification for baseline characteristics with risk of EC/EIN in pre- and perimenopausal women with AUB, underscoring the need for biomarkers that can improve risk stratification in this population. While it goes ae scope of this manuscript to evaluate the clinical management of benign causes of abnormal bleeding (e.g., uterine polyps), this will be an important future analysis in our cohort.

Strengths and Limitations

A unique strength of our study is that we enrolled a large clinical population of women with abnormal bleeding undergoing diagnostic evaluation for EC that enables evaluation of risk assessment strategies in this population. Our population is ideally suited to evaluate promising clinical risk models, and ongoing biospecimen collections will enable integration of biomarkers with clinical and epidemiologic risk factors to determine optimal approaches for risk assessment.[21] While our study had excellent disease ascertainment, 10% of women did not have endometrial biopsy. We assume that risk among these women is low; however, we cannot rule out the possibility of an underlying EC/EIN diagnosis. It is possible that some patients diagnosed as having a benign endometrium may have a subsequent diagnosis of EC/EIN. Prospective follow-up is a central component of our study and as data become available, they will inform how much reassurance a negative biopsy can provide. Despite a large sample size, the prevalence of EC and EIN in this population were still low, limiting our power to estimate risks with sufficient precision for some scenarios. Further, while our study population reflects real-world clinical practice, results may not be generalizable to other, particularly racially-diverse populations.

Conclusions

In conclusion, we introduce a risk-based approach to guide clinical management and to support evaluation of new biomarkers and risk tools as they are developed.[13] We show that using an age cutoff of 60 years improves risk stratification of TVUS in women with PMB. Currently recommended practice does not align with risk of endometrial cancer observed in

our study. Risk estimates from our study can serve as a benchmark for future studies of new biomarkers and/or risk prediction tools to assess their clinical significance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

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AJOG at a Glance:

A. **Why was the study conducted?** To assess the clinical utility of strategies for endometrial cancer detection, we applied a risk-based approach to evaluate diagnostic tests and recommended clinical management algorithms to inform clinical decision-making in a population of women with abnormal bleeding at the Mayo Clinic.

B. **What are the key findings?** The prevalence of endometrial cancer was 7.9% (47/593) among postmenopausal women and 1.2% (7/570) among pre- or perimenopausal women. Among postmenopausal women with an initial bleeding episode in whom transvaginal ultrasound is recommended, endometrial thickness did not provide meaningful risk stratification. As demonstrated by our example using age with a cutoff of 60 years, clinical variables may improve risk stratification compared to current clinical practice.

C. **What does this study add to what is already known?** Current clinical recommendations for endometrial cancer detection may not be consistent with underlying risk.
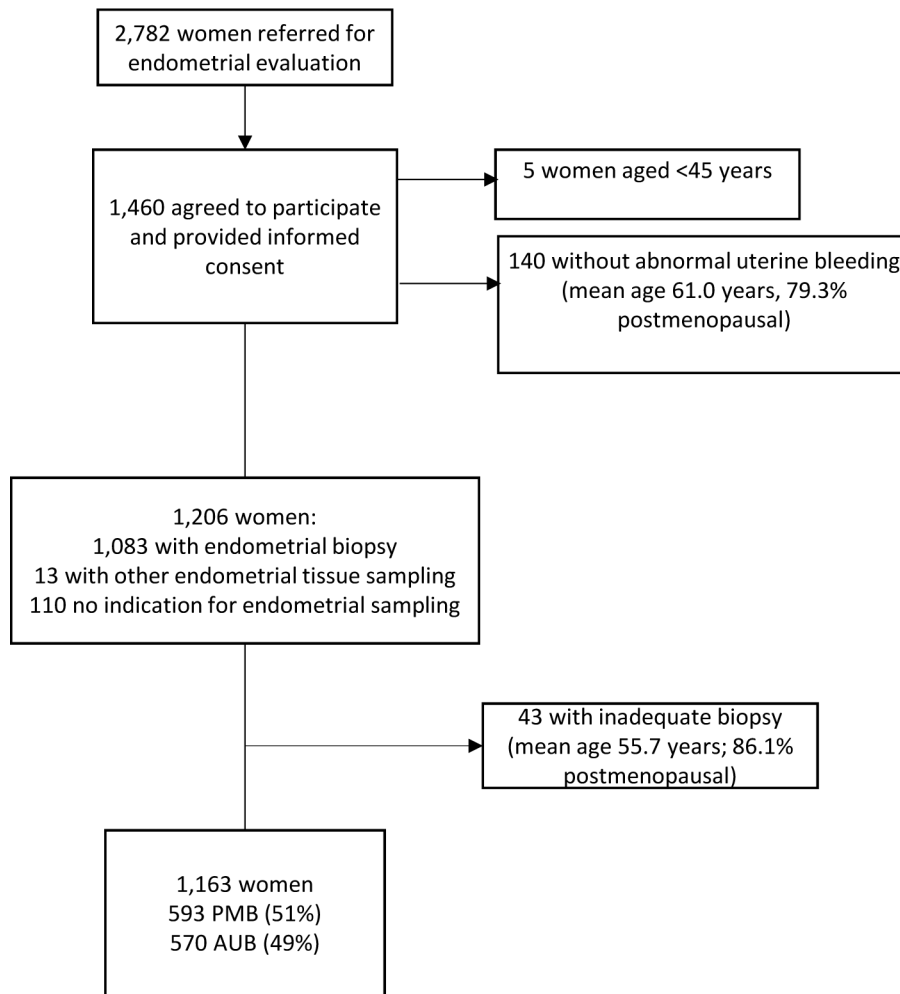
Figure 1.
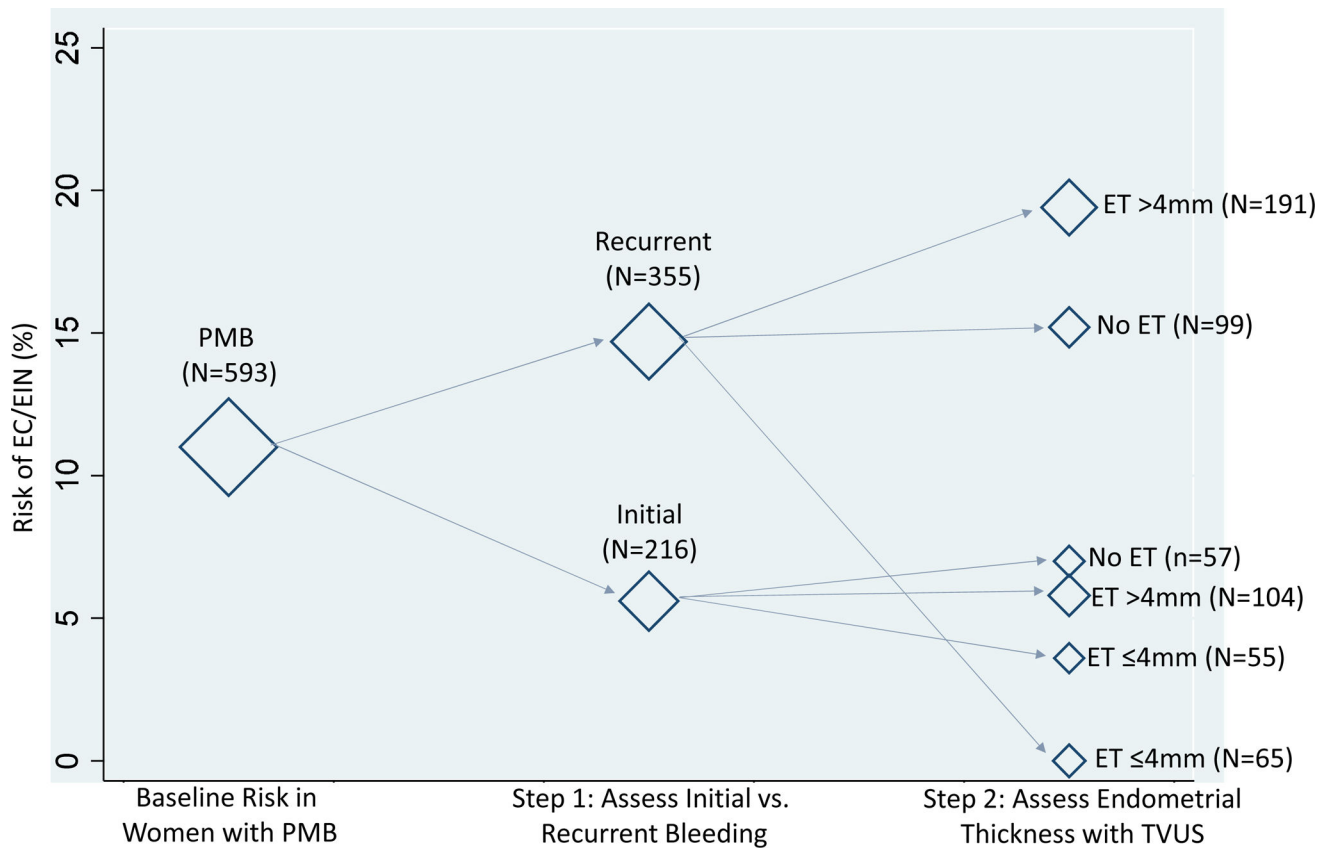CONSORT Diagram of the study population

Figure 2. Baseline Risk of Endometrial Cancer and Endometrial Intraepithelial Neoplasia according to bleeding type and endometrial thickness.

We evaluated the combined baseline risks of endometrial cancer and endometrial intraepithelial neoplasia combined following a sequential diagnostic process according to current guidelines from the American College of Obstetricians and Gynecologists[11]. Bleeding type was characterized as either initial episode of bleeding or recurrent bleeding (any occurrence of bleeding after prior evaluation for PMB). Endometrial thickness was measured clinically using transvaginal ultrasound. The diamond markers are weighted according to the corresponding number of women within each stratum of diagnostic test results. A total of 22 women are missing bleeding type information; the risk of EC/EIN in these women is 4.6%. Abbreviations: EC, endometrial cancer; EIN, Endometrial Intraepithelial Neoplasia; PMB, postmenopausal bleeding; ET, endometrial thickness; TVUS, transvaginal ultrasound
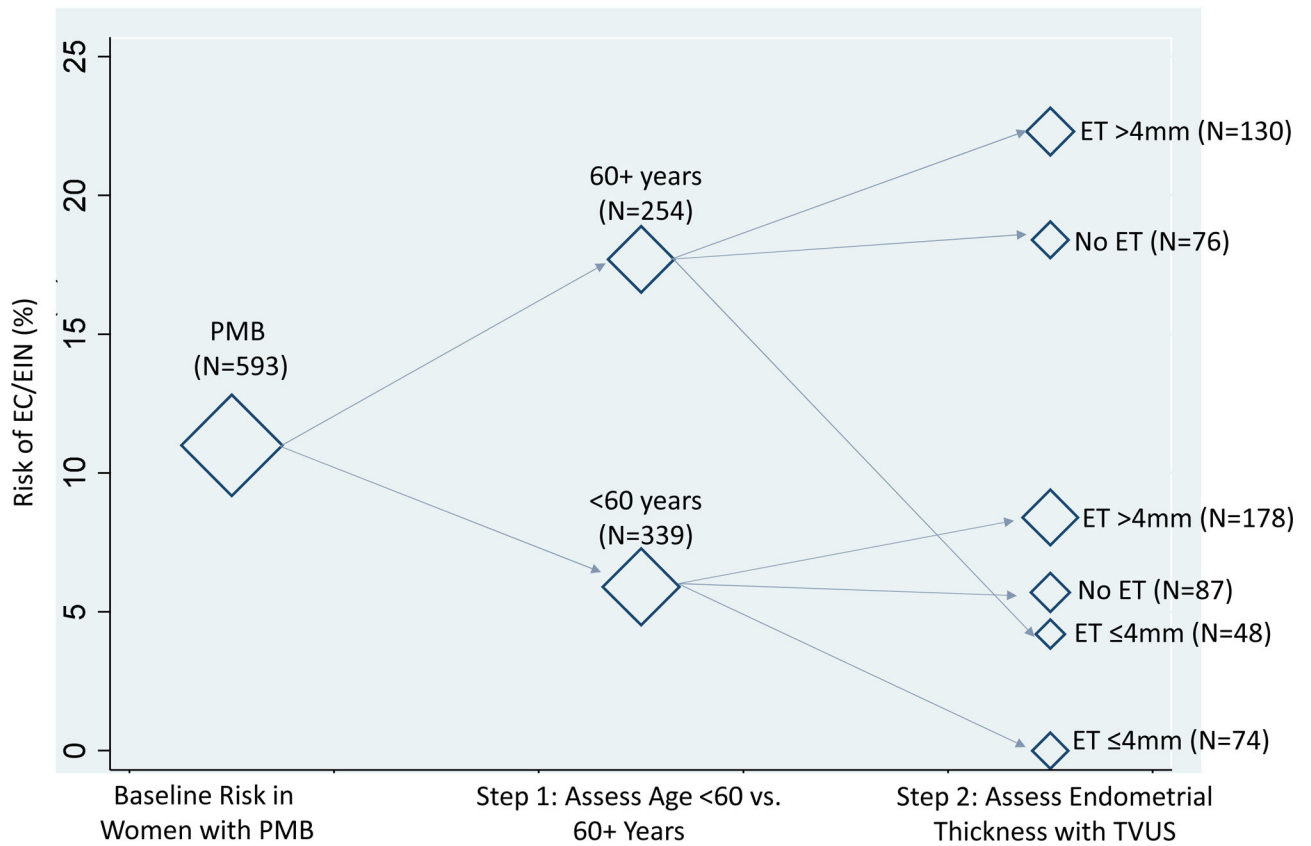
Figure 3. Baseline Risk of Endometrial Cancer and Endometrial Intraepithelial Neoplasia according to age and endometrial thickness.

We evaluated the combined baseline risks of endometrial cancer and endometrial intraepithelial neoplasia combined using age at a cutoff of 60 years (<60 and 60) as an initial risk stratifier. Endometrial thickness was measured clinically using transvaginal ultrasound. The diamond markers are weighted according to the corresponding number of women within each stratum of diagnostic test results. Abbreviations: EC, endometrial cancer; EIN, Endometrial Intraepithelial Neoplasia; PMB, postmenopausal bleeding; ET, endometrial thickness; TVUS, transvaginal ultrasound

Table 1.

Baseline Characteristics Among Women with Abnormal Uterine Bleeding by Menopausal Status

	Postmenopausal Women (PMB)				Premenopausal Women (AUB)			
	Total	Benign	EINEn	EC	Total	Benign	EINEIN	EC
Total	593 (100.0)	528 (89.0)	18 (3.0)	47 (7.9)	570 (100.0)	555 (97.4)	8 (1.4)	7 (1.2)
Age Group*								
<60 years	339 (57.2)	319 (94.1)	10 (3.0)	10 (3.0)				
60+ years	254 (42.8)	209 (82.3)	8 (3.1)	37 (14.6)				
Age Group								
<50 years					301	296 (98.3)	1 (0.3)	4 (1.3)
50+ years					269	259 (96.3)	7 (2.6)	3 (1.1)
Race/Ethnicity								
Non-Hispanic White	557 (93.9)	498 (89.4)	17 (3.1)	42 (7.5)	527 (92.5)	512 (97.2)	8 (1.5)	7 (1.3)
Non-Hispanic Black	5 (0.8)	4 (80.0)	0 (0.0)	1 (20.0)	6 (1.0)	6 (100.0)	0 (0.0)	0 (0.0)
Hispanic	8 (1.4)	7 (87.5)	1 (12.5)	0 (0.0)	10 (1.8)	10 (100.0)	0 (0.0)	0 (0.0)
Other	23 (3.9)	19 (82.6)	0 (0.0)	4 (17.4)	27 (4.7)	27 (100.0)	0 (0.0)	0 (0.0)
Body Mass Index*								
Normal	167 (28.4)	159 (95.2)	0 (0.0)	8 (4.8)	176	173 (98.3)	1 (0.6)	2 (1.1)
Overweight	165 (28.1)	151 (91.5)	1 (0.6)	13 (7.9)	167	166 (99.4)	0 (0.0)	1 (0.6)
Obese	256 (43.5)	214 (83.6)	17 (6.6)	25 (9.8)	224	213 (95.1)	7 (3.1)	4 (1.8)
Current Hormone Use*								
No	415 (70.1)	357 (86.0)	16 (3.9)	42 (10.1)	513	499 (97.3)	7 (1.4)	7 (1.4)
Yes	177 (29.9)	170 (96.1)	2 (1.1)	5 (2.8)	55	54 (98.2)	1 (1.8)	0 (0.0)
Type II Diabetes*								
No	542 (91.4)	494 (91.1)	12 (2.2)	36 (6.6)	544	530 (97.4)	8 (1.5)	6 (1.1)
Yes	51 (8.6)	32 (66.7)	6 (11.8)	11 (21.6)	26	25 (96.2)	0 (0.0)	1 (3.9)
Smoking Status								
Never	391 (65.9)	345 (88.2)	10 (2.6)	36 (9.2)	410	399 (97.3)	5 (1.2)	6 (1.5)
Former	166 (6.1)	149 (89.8)	7 (4.2)	10 (6.0)	118	114 (96.6)	0 (0.0)	0 (0.0)
Current	36 (28.0)	34 (94.4)	1 (2.8)	1 (2.8)	41	41 (100.0)	3 (2.5)	1 (0.9)
Past OC Use								
No	163 (28.9)	140 (85.9)	8 (4.9)	15 (9.2)	134	129 (96.3)	2 (1.5)	3 (2.2)
Yes	402 (71.1)	366 (91.0)	9 (2.2)	27 (6.7)	427	418 (97.9)	5 (1.2)	4 (0.9)
Parity#								
Nulliparous	95 (16.0)	84 (88.4)	3 (3.2)	8 (8.4)	91	85 (93.4)	3 (3.3)	3 (3.3)
Parous	498 (84.0)	444 (89.2)	15 (3.0)	39 (7.8)	478	469 (98.1)	1 (1.1)	4 (0.8)
Bleeding Amount (PMB)								
Spotting	277 (47.6)	241 (87.0)	9 (3.3)	27 (9.8)				
Light	184 (31.6)	169 (91.9)	5 (2.7)	10 (5.4)				

	Postmenopausal Women (PMB)				Premenopausal Women (AUB)			
	Total	Benign	EINEn	EC	Total	Benign	EINEIN	EC
Heavy	94 (16.2)	83 (88.3)	2 (2.1)	9 (9.6)				
Other/Not specified	27 (4.6)	25 (92.6)	1 (3.7)	1 (3.7)				
Recurrent Bleeding *(PMB)								
No	216 (37.8)	204 (94.4)	1 (0.5)	11 (5.1)				
Yes	355 (62.2)	303 (85.4)	16 (4.5)	36 (10.1)				
Bleeding Type (AUB)								
Heavy menstrual bleeding					183	180 (98.4)	3 (1.6)	0 (0.0)
Intermenstrual bleeding					123	121 (98.4)	0 (0.0)	2 (1.6)
Menometrorrhagia					216	206 (95.4)	5 (2.3)	5 (2.3)
Irregular menses					27	27 (100.0)	0 (0.0)	0 (0.0)
Other AUB					21	21 (100.00	0 (0.0)	0 (0.0)
Endometrial Thickness >4mm *								
No	122 (20.6)	120 (98.4)	0 (0.0)	2 (1.6)	50	50 (100.0)	0 (0.0)	0 (0.0)
Yes	308 (51.9)	264 (85.7)	13 (4.2)	31 (10.1)	294	283 (96.3)	6 (2.0)	5 (1.7)
Missing/Not Done	163 (27.5)	144 (88.3)	5 (3.1)	14 (8.6)	226	222 (98.2)	2 (0.9)	2 (0.9)

*
Chi2 p-value <0.05 for women with PMB;

#
Chi-sq p-value for women with AUB

Abbreviations: PMB, postmenopausal bleeding; AUB, abnormal uterine bleeding; EC, endometrial cancer; EIN, Endometrial Intraepithelial Neoplasia; OC, oral contraceptives

Table 2.

Simulated Clinical Efficiency of Algorithms for Diagnostic Evaluation Among Women Presenting to Mayo Clinic with PMB and AUB

Referral Algorithm	Immediate Biopsy	No Biopsy	Women with Biopsy (%)	EC/EIN Detected (%)	EC/EIN Missed (%)	Biopsies per EC/EIN Detected (%)
1. Biopsy	All with PMB		100%	100%	0	9.7
2. TVUS in women with initial bleeding	Recurrent bleeding; Initial bleeding with ET >4mm	Initial bleeding, ET ≤4mm	87.3%	96.7%	3.3%	6.7
3. TVUS in women aged <60 years	Aged 60+ years; Aged <60 years with ET >4mm	Aged <60 years, ET ≤4mm	82.0%	100%	0%	5.9
1. Biopsy	All with AUB 45+ years		100%	100%	0	38

Abbreviations: PMB, postmenopausal bleeding; TVUS, transvaginal ultrasound; ET, endometrial thickness; AUB, abnormal uterine bleeding; EC, endometrial cancer; EIN, Endometrial Intraepithelial Neoplasia