Thai Journal of Obstetrics and Gynaecology
March 2025, Vol. 33, No. 2, pp. 95-103.

## GYNAECOLOGY

# Age-associated with Endometrial Intraepithelial Neoplasia and Endometrial Carcinoma in Patients with Abnormal Uterine Bleeding

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## ABSTRACT

**Objectives:** To determine the age cut-off for endometrial biopsy in women with abnormal uterine bleeding to detect endometrial intraepithelial neoplasia and endometrial carcinoma in patients with abnormal uterine bleeding.

**Materials and Methods:** A total of 1,384 women presenting with abnormal uterine bleeding underwent endometrial biopsy at Maharat Nakhon Ratchasima Hospital between July 1, 2021, and June 30, 2023. This retrospective cohort study collected age and other risk factors of endometrial intraepithelial neoplasia and endometrial carcinoma, then calculated sensitivity, specificity, negative likelihood ratio, area under the curve (AUC) of each age cut-off and conducted multivariable logistic regression.

**Results:** The age group ≥ 45 years showed a moderate impact negative likelihood ratio (0.14, 95% confidence interval 0.07 - 0.31) and higher AUC (0.91) compared to other age groups, with a sensitivity of 94.17% and a specificity of 41.06%. The risk factors including age ≥ 45 years, nulliparity, menopause status, diabetes mellitus, polycystic ovarian syndrome, endometrial thickness of 4 and 7 mm or thicker were significantly associated with endometrial intraepithelial neoplasia and endometrial carcinoma.

**Conclusion:** Consider endometrial biopsy for screening of endometrial intraepithelial neoplasia and endometrial carcinoma in women aged 45 or older with abnormal uterine bleeding or those under 45 with risk factors such as nulliparity, diabetes mellitus, menopausal status, polycystic ovarian syndrome, and endometrial thickness of 4 and 7 mm or thicker.

**Keywords:** age, endometrial intraepithelial neoplasia, endometrial cancer, abnormal uterine bleeding, endometrial biopsy

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**Received:** 14 August 2024, **Revised:** 24 October 2024, **Accepted:** 25 November 2024

# *อายุที่สัมพันธ์กับภาวะเยื่อบุโพรงมดลูกหนาตัวผิดปกติและมะเร็งเยื่อบุโพรงมดลูกในผู้ป่วยที่มีเลือดออกผิดปกติจากโพรงมดลูก*

***พิชญ์สินี สบายยิ่ง, ฐิตินันท์ สมุทรไชยกิจ, ดวงพร รัตนลาภไพบูลย์, ชญานิษฐ์ เดชวงศ์ญา***

***บทคัดย่อ***

***วัตถุประสงค์:*** *เพื่อกำหนดจุดตัดอายุที่เหมาะสมสำหรับการดูดชิ้นเนื้อเยื่อบุโพรงมดลูก (endometrial biopsy) ในผู้ป่วยหญิงที่มีเลือดออกผิดปกติจากโพรงมดลูก เพื่อคัดกรองภาวะเยื่อบุโพรงมดลูกหนาผิดปกติ และมะเร็งเยื่อบุโพรงมดลูก*

***วัสดุและวิธีการ:*** *เป็นการศึกษาแบบย้อนหลังในผู้ป่วยหญิงที่มีเลือดออกผิดปกติจากโพรงมดลูกและได้รับการดูดชิ้นเนื้อเยื่อบุโพรงมดลูก (endometrial biopsy) จำนวน 1,384 คน ที่เข้ารับการรักษาในโรงพยาบาลมหาราชนครราชสีมา ตั้งแต่ 1 กรกฎาคม พ.ศ. 2564 ถึง วันที่ 30 มิถุนายน พ.ศ. 2566 โดยรวบรวมอายุและปัจจัยเสี่ยงในการเกิดภาวะเยื่อบุโพรงมดลูกหนาผิดปกติ และมะเร็งเยื่อบุโพรงมดลูกที่บันทึกในเวชระเบียน คำนวณหาความไว (sensitivity) ความจำเพาะ (specificity) ความน่าจะเป็นเมื่อแบบทดสอบเป็นลบ (negative likelihood ratio) และพื้นที่ใต้กราฟ (area under curve) ของแต่ละจุดตัดอายุ รวมถึงวิเคราะห์การถดถอยเชิงพหุ*

***ผลการศึกษา:*** *ในกลุ่มอายุ 45 ปีขึ้นไป มีความน่าจะเป็นเมื่อแบบทดสอบเป็นลบ (negative likelihood ratio) อยู่ในระดับ moderate (0.14, 95% confidence interval 0.07 - 0.31) และมีพื้นที่ใต้กราฟ (area under curve) 0.91 ซึ่งสูงกว่ากลุ่มอายุอื่น ร่วมกับมีความไว (sensitivity) ร้อยละ 94.17 และความจำเพาะ (specificity) ร้อยละ 41.06 นอกจากนี้พบว่าปัจจัยที่สัมพันธ์การเกิดภาวะเยื่อบุโพรงมดลูกหนาผิดปกติและมะเร็งเยื่อบุโพรงมดลูกอย่างมีนัยสำคัญคือ อายุ 45 ปีขึ้นไป ไม่เคยมีบุตร ภาวะหมดระดู โรคเบาหวาน ภาวะถุงน้ำรังไข่หลายใบ ภาวะเยื่อบุโพรงมดลูกหนา 4 หรือ 7 มิลลิเมตรขึ้นไป*

***สรุป:*** *พิจารณาใช้อายุ 45 ปี ขึ้นไป เป็นจุดตัดในการคัดกรองผู้ป่วยหญิงที่มีเลือดออกผิดปกติจากโพรงมดลูก ด้วยการดูดชิ้นเนื้อในโพรงมดลูก และส่งตรวจทางพยาธิวิทยา เนื่องจากสัมพันธ์กับภาวะเยื่อบุโพรงมดลูกหนาตัวผิดปกติและมะเร็งเยื่อบุโพรงมดลูก หรือพิจารณาคัดกรองในผู้ป่วยหญิงที่อายุน้อยกว่า 45 ปี ที่มีปัจจัยเสี่ยงของการเกิดภาวะเยื่อบุโพรงมดลูกหนาผิดปกติและมะเร็งเยื่อบุโพรงมดลูก ได้แก่ ไม่เคยมีบุตร โรคเบาหวาน ภาวะหมดระดู ภาวะถุงน้ำรังไข่หลายใบ เยื่อบุโพรงมดลูกหนา 4 หรือ 7 มิลลิเมตรขึ้นไป*

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## Introduction

Endometrial cancer is a common gynecologic malignancy. In 2023, there were 66,200 new cases of endometrial cancer and 13,030 deaths in the United States, accounting for 2.1% of all endometrial cancer cases[1]. In Thailand, endometrial cancer ranks as the second most common gynecologic malignancy, following cervical cancer as the most prevalent[2].

Endometrial hyperplasia is a precancerous lesion of endometrial cancer[3] caused by prolonged exposure to unopposed estrogen. Risk factors of endometrial hyperplasia include late menopause, obesity, diabetes mellitus, unopposed estrogen, and the use of tamoxifen[4]. Endometrial hyperplasia and endometrial cancer often manifest as abnormal uterine bleeding, and these conditions can be detected early through histological examination.

The American College of Obstetricians and Gynecologists (ACOG) recommends considering endometrial biopsy for women experiencing abnormal uterine bleeding who are aged 45 or older, or for those under 45 with risk factors such as obesity, polycystic ovarian syndrome, unsuccessful treatment, and persistent abnormal uterine bleeding[5].

While the Society of Obstetricians and Gynaecologists of Canada suggests that endometrial biopsy be considered for women aged 40 and older, as well as for those under 40 who have risk factors for endometrial cancer, such as nulliparity, body mass index (BMI) over 30 kg/m$^2$, polycystic ovarian syndrome, diabetes mellitus, history of hereditary nonpolyposis colorectal cancer (HNPCC), failed medication, and significant intermenstrual bleeding[6].

The recommendation for endometrial biopsy from different countries may have been suggested at different ages, and currently, there is no standard screening for endometrial cancer. In this study, we aimed to determine the age cut-off for endometrial biopsy to detect endometrial intraepithelial neoplasia and endometrial cancer in women presenting with abnormal uterine bleeding at Maharat Nakorn Ratchasima Hospital, as well as other risk factors such as BMI, menopausal status, polycystic ovarian syndrome, diabetes mellitus, hypertension, tamoxifen use, and dyslipidemia.

## Materials and Methods

A retrospective cohort study, authorized by the institutional review board of Maharat Nakhon Ratchasima, examined the data of patients who presented with abnormal uterine bleeding and underwent endometrial biopsy for histology between July 1, 2021, and June 30, 2023. The abnormal histology included endometrial intraepithelial neoplasia and endometrial carcinoma, while the remaining cases were categorized as the less-than endometrial intraepithelial neoplasia (EIN) group. Because endometrial hyperplasia without atypia can develop into endometrial cancer at a rate of 5% in 20 years[7], or it can regress spontaneously, we classify it as less-than EIN group.

The sample size was calculated using the model literature developed by Corbacioglu Esmer et al[8]. The study revealed a 67.5% sensitivity in detecting endometrial hyperplasia with atypia and endometrial cancer in individuals aged 45 years or older. Therefore, a statistical formula was employed to calculate the proportion for the infinite population. At least 85 patients in the endometrial intraepithelial neoplasia and endometrial cancer group were required. Our pilot study, conducted from July 2021 to June 2022, indicated that 54 out of 760 patients presenting with abnormal uterine bleeding were diagnosed with endometrial cancer, accounting for 7.1%. Therefore, a sample size of 1,196 patients presenting with abnormal uterine bleeding who will undergo endometrial biopsy was required.

Women with abnormal uterine bleeding who had undergone endometrial biopsy at the age of 30 years or older during the study period were included. Patients were excluded if there was incomplete data, inability to interpret histology through endometrial biopsy, pregnancy, coagulopathy, or use of anticoagulant drugs. We gathered data on age, BMI, diabetes mellitus, hypertension, dyslipidemia, menopausal status, hormonal contraception use,

tamoxifen use, polycystic ovarian syndrome, and endometrial thickness.

Data were analyzed by STATA version 17.0 to determine sensitivity, specificity, negative likelihood ratio, and area under the curve. Multivariable logistic regression analysis was utilized to calculate associated factors of EIN and endometrial cancer, providing an adjusted odds ratio. A p value of < 0.05 was considered significant.

## Results

A total of 1,658 women presented with abnormal uterine bleeding underwent endometrial biopsy at Maharat Nakorn Ratchasima Hospital. One hundred seventy-two women were excluded due to incomplete data, and 102 were excluded due to challenges in histology interpretation. As a result, the study included 1,384 women, which comprised 1,236 cases of normal histology, 45 cases of hyperplasia without atypia, 15 cases of endometrial intraepithelial hyperplasia, and 88 cases of endometrial cancer.

The demographic data presented in Table 1 revealed significant differences in age, BMI, parity, endometrial thickness, hypertension, diabetes mellitus, dyslipidemia, and hormonal contraception use between the EIN and endometrial cancer groups compared to the less-than-EIN group. However, there were no significant differences in polycystic ovarian syndrome and tamoxifen use. Additionally, the mean age was 46 years in the less-than-EIN group and 61 years in the endometrial intraepithelial hyperplasia and endometrial carcinoma group.

**Table 1.** Demographic characteristics.

| Characteristic | EIN and Endometrial CA (n = 103) | Less than EIN (n = 1,281) | p value |
|---|---|---|---|
| Age | | | < 0.001* |
| < 35 years | 2 (1.94) | 46 (3.59) | |
| 35 - 39 years | 2 (1.94) | 161 (12.57) | |
| 40 - 44 years | 2 (1.94) | 319 (24.90) | |
| 45 - 49 years | 11 (10.68) | 373 (29.12) | |
| ≥ 50 years | 86 (83.50) | 382 (29.82) | |
| BMI | | | < 0.001* |
| < 23 | 30 (29.1) | 600 (46.8) | |
| 23 - 27.49 | 34 (33.0) | 385 (30.1) | |
| ≥ 27.5 | 39 (37.9) | 296 (23.1) | |
| Parity | | | < 0.001* |
| 0 | 25 (24.3) | 196 (15.3) | |
| 1 - 2 | 40 (38.8) | 831 (64.9) | |
| > 2 | 38 (36.9) | 254 (19.8) | |
| Menopause status | 79 (76.7) | 238 (18.6) | < 0.001* |
| Hypertension | 58 (56.3) | 295 (23.0) | < 0.001* |
| Diabetes mellitus | 40 (38.8) | 143 (11.2) | < 0.001* |
| Dyslipidemia | 39 (37.9) | 169 (13.2) | < 0.001* |
| Hormonal use | 1 (1.0) | 131 (10.2) | 0.002* |
| PCOS | 3 (2.9) | 16 (1.3) | 0.163 |
| Tamoxifen | 2 (1.9) | 15 (1.2) | 0.494 |
| Endometrial thickness | | | < 0.001* |
| < 4 mm | 9 (8.7) | 587 (45.8) | |
| 4 - 6.9 mm | 14 (13.6) | 199 (15.5) | |
| ≥ 7 mm | 80 (77.7) | 495 (38.7) | |

Data are shown as n (%)
EIN: endometrial intraepithelial neoplasia, CA: cancer, BMI: body mass index, PCOS: polycystic ovary syndrome
*p < 0.05 was considered statistically significant

When using age as the cut-off, the prevalence of endometrial intraepithelial neoplasia and endometrial cancer was highest in age ≥ 50 years group, followed by the age ≥ 45 years group (Table 2). Furthermore, when analyzing the age group, we found the percentage of endometrial intraepithelial hyperplasia and endometrial carcinoma cases of each age group (Fig 1).

**Table 2.** The prevalence of cut-off age in endometrial carcinoma and endometrial intraepithelial neoplasia.

| Cut-off age (years) | Number of Patients (n) | Number of Endometrial cancer and EIN | Prevalence |
|---|---|---|---|
| ≥ 35 | 1,366 | 101 | 7.39% |
| ≥ 40 | 1,173 | 99 | 8.44% |
| ≥ 45 | 852 | 97 | 11.38% |
| ≥ 50 | 468 | 86 | 18.38% |

* The proportion of endometrial intraepithelial neoplasia and endometrial carcinoma to number of patients in each age group
EIN: endometrial intraepithelial neoplasia

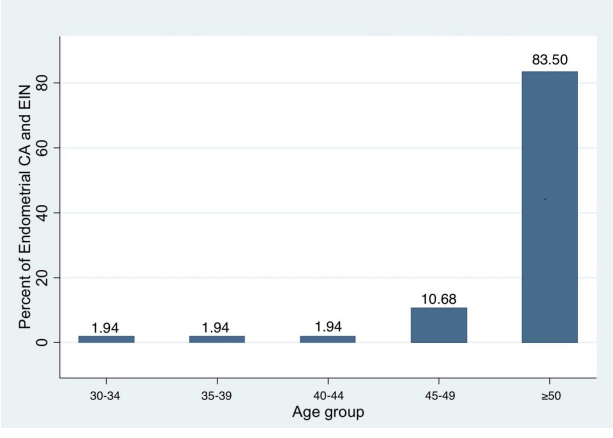



**Fig. 1.** The percentage of endometrial carcinoma and endometrial intraepithelial neoplasia in each age group.

However, the age ≥ 35 years had the highest sensitivity (98.1%, 95% confidence interval 0.93 - 0.99), followed by age ≥ 40 years, age ≥ 45 years, and age ≥ 50 years. In terms of specificity, we found that age ≥ 50 years had the highest specificity (70.18%, 95%CI 0.68 - 0.73), followed by age ≥ 45 years, age ≥ 40 years, and age ≥ 35 years. Concerning the negative likelihood ratio, we found that age ≥ 45 years had a moderate effect (0.14, 95%CI 0.07 - 0.31), while age ≥ 40 years and age ≥ 50 years had a small effect, and age ≥ 35 years had a minimal effect. Furthermore, our study revealed that age ≥ 50 years had the highest area under the curve (0.77), followed by age ≥ 45 years (0.68) (Table 3).

The research identified several factors associated with endometrial intraepithelial hyperplasia and endometrial carcinoma. By applying multiple logistic regression analysis to control for confounding variables, the study highlighted the following statistically significant factors, including age ≥ 45 years, nulliparity, menopause, diabetes, and endometrial thicknesses of 4-6.9 mm and 7 mm or more. Although polycystic ovarian syndrome initially appeared to be statistically insignificant, it was later determined to significantly increase the risk, after excluding other confounding variables (Table 4). Lastly, controlling other factors from this model, our study revealed that age ≥ 45 years had the highest area under the curve (0.9144).

**Table 3.** The sensitivity, specificity, negative likelihood ratio, and area under the receiver operating characteristic curve in endometrial carcinoma and endometrial intraepithelial neoplasia.

| Cut-point age (years) | ≥ 35 | ≥ 40 | ≥ 45 | ≥ 50 |
|---|---|---|---|---|
| Negative LR | 0.54 | 0.24 | 0.14 | 0.24 |
| (95% CI) | (0.13-2.20) | (0.09 – 0.63) | (0.07 – 0.31) | (0.15 – 0.36) |
| Sensitivity | 98.1% | 96.12% | 94.17% | 83.50% |
| (95% CI) | (0.93-0.99) | (0.90 – 0.99) | (0.88 – 0.98) | (0.75 – 0.90) |
| Specificity | 3.6% | 16.16% | 41.06% | 70.18% |
| (95% CI) | (0.03-0.05) | (0.14 – 0.18) | (0.38 – 0.44) | (0.68 – 0.73) |
| AUC | 0.51 | 0.56 | 0.68 | 0.77 |
| (95% CI) | (0.49 - 0.52) | (0.54 – 0.58) | (0.65 – 0.70) | (0.73 – 0.81) |

AUC: area under the receiver operating characteristic curve, EIN: endometrial intraepithelial neoplasia, LR: likelihood ratio, CI: confidence interval

**Table 4.** Logistic regression of factors associated with endometrial cancer and endometrial intraepithelial neoplasia.

| Outcome | Odd ratio | p value | Adjusted odd ratio | p value |
|---|---|---|---|---|
| Age ≥ 45 years | 11.26 (4.90, 25.88) | < 0.001 | 4.86 (1.74, 13.55) | 0.003* |
| BMI | | | | |
| < 23 | 1 | | 1 | |
| 23-27.49 | 1.77 (1.06, 2.93) | 0.028 | 1.59 (0.87, 2.89) | 0.130 |
| ≥ 27.5 | 2.64 (1.60, 4.33) | < 0.001 | 1.72 (0.94, 3.16) | 0.081 |
| Parity | | | | |
| 0 | 2.65 (1.57, 4.47) | < 0.001 | 3.11 (1.65, 5.87) | < 0.001* |
| 1-2 | 1 | | 1 | |
| > 2 | 3.11 (1.95, 4.95) | < 0.001 | 1.67 (0.97, 2.89) | 0.065 |
| Menopause status | 14.43 (8.94, 23.27) | < 0.001 | 7.93 (4.42, 14.20) | < 0.001* |
| Hypertension | 4.31 (2.86, 6.49) | < 0.001 | 1.28 (0.71, 2.29) | 0.412 |
| Diabetes mellitus | 5.05 (3.28, 7.79) | < 0.001 | 2.35 (1.29, 4.31) | 0.006* |
| Dyslipidemia | 4.01 (2.61, 6.16) | < 0.001 | 1.26 (0.69, 2.32) | 0.454 |
| Hormonal use | 0.09 (0.01, 0.62) | 0.015 | 0.46 (0.06, 3.62) | 0.463 |
| PCOS | 2.37 (0.68, 8.28) | 0.176 | 10.43 (2.32, 46.84) | 0.002* |
| Tamoxifen | 1.67 (0.38, 7.41) | 0.499 | 0.44 (0.09, 2.15) | 0.311 |
| Endometrial thickness | | | | |
| < 4 mm | 1 | | 1 | |
| 4-6.9 mm | 4.59 (1.96, 10.76) | < 0.001 | 4.96 (1.97, 12.47) | 0.001* |
| ≥ 7 mm | 10.54 (2.24, 21.21) | < 0.001 | 10.25 (4.85, 21.66) | < 0.001* |

*p < 0.05 was considered statistically significant

EIN: endometrial intraepithelial neoplasia, BMI: body mass index, PCOS: polycystic ovary syndrome

# Discussion

Age is frequently a crucial factor in determining whether to conduct an endometrial biopsy in patients who are experiencing abnormal uterine bleeding when there are no other possible risk factors. Most institutions recommend starting an endometrial biopsy in women with abnormal uterine bleeding at the age of 35-45 to detect the abnormal endometrial pathology. ACOG 2019[5] and The Royal Thai College of Obstetricians and Gynaecologists (RTCOG) 2022[9] suggest starting at age 45, whereas other studies indicate screening at 35[10, 11] and 40[8]. As a result,

there is uncertainty about the cut-off age for endometrial biopsy screening to detect abnormal endometrial pathology.

This study found that the prevalence of endometrial intraepithelial neoplasia and endometrial cancer was higher when using cut-off ages of 40 and 45, ranging from 8.44% to 11.38%. This was increased compared to using cut-off ages of 35 and 40 years, which ranged from 7.54% to 8.44%. Notably, 11 women in the 45-49 age group were diagnosed with EIN or endometrial cancer, compared to two women each in the 30-34, 35-39 and 40-44 age groups.

When using age as a cut-off for deciding on endometrial biopsy in women who present with abnormal uterine bleeding without considering other risk factors, age ≥ 45 years had significantly higher specificity than age ≥ 40 years, while the sensitivities remained similar. Higher specificity reduces the chance of false positive rates in women without abnormal endometrial pathology, therefore avoiding unnecessary endometrial biopsy and increasing cost-effectiveness compared to the group with lower specificity.

Comparing age groups, those aged ≥ 35 years had the lowest specificity, while those aged ≥ 50 years had the lowest sensitivity. Therefore, utilizing ages ≥ 35 and ≥ 50 years as cut-offs is unsuitable. Setting the age cut-off at 35 years would result in more unnecessary endometrial biopsies, whereas setting it at age 50 years would lead to a higher false negative rate, missing EIN or endometrial cancer in many cases. Therefore, utilizing an age ≥ 45 years is the most appropriate cut-off for screening endometrial biopsy in women with abnormal uterine bleeding.

When considering the negative likelihood ratio, it was found that setting the age cutoff at ≥ 45 years has a moderate impact. This indicated that patients under the age of 45 presenting with abnormal uterine bleeding and having normal histopathological results were less likely to develop endometrial cancer or endometrial intraepithelial neoplasm compared to other cut-off points with minimal or small effects. In terms of the area under the curve (AUC), after adjusting for other potential confounding variables, it was found that the AUC for people aged ≥ 45 years was a good level and the highest (0.9144). Although not significantly different from other age cutoffs, it consistently performed well across all age cut-offs.

Among patients under the age of 45, there were four cases of endometrial cancer and two cases of endometrial intraepithelial neoplasm. Each individual had risk factors for developing endometrial intraepithelial neoplasm and endometrial cancer higher than those in the general population. For instance, the first endometrial cancer case had an abnormal papanicolaou smear result atypical glandular cells (AGC), the second case had morbid obesity (BMI 70 kg/m$^2$), diabetes mellitus at young age, and polycystic ovarian syndrome, the third case had obesity (BMI 34.63 kg/m$^2$), diabetes mellitus at young age, and nulliparity, and the fourth case had morbid obesity (BMI 39.13 kg/m$^2$) and diabetes mellitus at young age. In patients with endometrial intraepithelial neoplasm, one was obese (BMI 29.97 kg/m$^2$), nulliparous, and had polycystic ovarian syndrome, while the other was obese (BMI 30.4 kg/m$^2$) and also had polycystic ovarian syndrome. From this study, patients under the age of 45 with abnormal histopathology, such as endometrial intraepithelial neoplasm and endometrial cancer, had significantly higher risk factors compared to the general population.

This study selected an age cut-off of ≥ 45 years, which aligns with the RTCOG 2022[9] and ACOG 2019[5] recommendations for endometrial biopsy, disregarding other risk factors. This was consistent with a study by Iram[12], which used an age cutoff of ≥ 45 years with a sensitivity of 70%, specificity of 63%, and an AUC of 0.646. However, this differed from a study conducted by Corbacioglu Esmer[8], which utilized a cut-off of ≥ 40 years. This difference might be due to ethnic diversity since their study population was European, while this study focused on an Asian population. There might be hidden risk factors that contribute to the development of endometrial cancer or endometrial intraepithelial neoplasm in the

population, which were not mentioned in their studies. Apart from age, other significant risk factors for endometrial intraepithelial neoplasm and endometrial cancer include nulliparity, diabetes, and menopause, which increase the risk by 4.69, 2.33, and 8.23, respectively. These findings aligned with studies by Jayawickcrama[13], Zhao[14], Özdemir[15], and Suwanwanich[10]. For polycystic ovarian syndrome, after controlling for other confounding variables, it was found to significantly increase the risk by 10.34, similar to a study by Barry[16], which found a significant increase of 2.79.

When assessing endometrial thickness, the average endometrial thickness in the less-than-EIN group was found to be 7 mm, consistent with a study by Van Den Bosch[17], which indicated that the thickness of atrophic endometrium can reach up to 7 mm. For this reason, this study established cut-off points at 4 mm and 7 mm, showing that endometrial thickness ≥ 4 mm and ≥ 7 mm significantly increases the risk by 4.96 and 10.25, respectively. These results were consistent with a study by Thoprasert[18] and Suwanwanich's studies[19] which reported endometrial thickness cut-off points at ≥ 8 mm and ≥ 10 mm, respectively. Interestingly, the optimal endometrial thickness cut-off values should be studies further.

In the study, obesity was noted to significantly increase the risk of developing endometrial intraepithelial neoplasm and endometrial cancer by 1.77 and 2.64, but after controlling for confounding variables such as diabetes and others, it was not statistically significant. In terms of hypertension and dyslipidemia, they were not found to statistically significantly increase the risk, in contrast to previous studies[14, 19, 20], which may be due to these three conditions acting as confounding factors for diabetes. Regarding the use of hormonal contraceptives and tamoxifen, after accounting for confounding variables, there was no statistically significant association, which contrasted with previous studies[19, 21, 22], possibly due to the small size of the population in this study using these medications.

A strength of this study was the utilization of electronic medical records data, which allowed for the retrospective gathering of age and assessing the risk of endometrial cancer. On the other hand, the study was limited as it is based on data from a single institution with retrospective data. Furthermore, the reliability of data such as contraceptive and tamoxifen use may be limited.

The benefits of this study were that it provided insight into the appropriate age for performing endometrial biopsy to minimize the risk of false negatives, ensuring the diagnosis of EIN and endometrial carcinoma. Additionally, it advocated avoiding unnecessary tissue biopsy in younger and low-risk patients, thereby increasing the cost-effectiveness of endometrial biopsy in the future. Moreover, future studies should explore the predictive scores to enhance the accuracy of selecting candidates for endometrial biopsy in women who present with abnormal uterine bleeding.

## Conclusion

The use of age ≥ 45 years as a cut-off for screening and conducting endometrial biopsy in women who present with abnormal uterine bleeding is recommended due to its high sensitivity, specificity, and favorable negative likelihood ratio. Even in cases where women are younger than 45 years but exhibit significant risk factors, including nulliparity, polycystic ovarian syndrome, diabetes mellitus, menopause, and an endometrial thickness of 4-7 mm or more, performing an endometrial biopsy is also advised.

## Acknowledgements

The authors would like to thank all the nurses and physician staff of the Department of Obstetrics and Gynecology, Maharat Nakhon Ratchasima Hospital.

## Potential conflicts of interest

The author declares no conflicts of interest.

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