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Risk Assessment of Endometrial Hyperplasia and Cancer in Premenopausal Women with Abnormal Uterine Bleeding

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ABSTRACT

Objectives: Our goal was to develop an endometrial sampling protocol for the early detection and treatment of endometrial hyperplasia and endometrial cancer (EH/EC) in premenopausal women experiencing abnormal uterine bleeding.

Materials and Methods: A prospective cohort study on premenopausal women with abnormal uterine bleeding who underwent endometrial sampling was conducted at Ratchaburi Hospital. Each patient's risk factors and conducted clinical assessments, including pelvic examinations and transvaginal ultrasound were documented. To determine the likelihood of EH/EC, univariate and stepwise logistic regression analyses were used.

Results: Among 200 eligible premenopausal women with abnormal uterine bleeding who received endometrial sampling, histological analysis identified EH in 14 women (7%) and EC in 7 women (3.5%). Stepwise logistic regression revealed a significant association of EH/EC with a body mass index of 30 kg/m^2 or higher, tamoxifen usage, and an endometrial thickness exceeding 10 mm ($p = 0.004$, 0.041, and 0.001, respectively). The presence of two or three of these risk factors significantly increased the association with EH/EC ($p < 0.001$).

Conclusion: Obesity, tamoxifen usage, and endometrial thickness greater than 10 mm were strong indicators of EH/EC. Endometrial sampling is recommended for patients exhibiting more than one of these risk factors.

Keywords: abnormal uterine bleeding, endometrial cancer, endometrial hyperplasia, endometrial sampling, model of endometrial sampling indication.

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การประเมินความเสี่ยงของภาวะเยื่อบุโพรงมดลูกหนาตัวผิดปกติ และมะเร็งโพรงมดลูก ในสตรีวัยก่อนหมดประจำเดือนที่มาด้วยเลือดออกผิดปกติจากโพรงมดลูก

มรกต สุวรรณวนิช

บทคัดย่อ

วัตถุประสงค์*: เพื่อหาข้อบ่งชี้ที่เหมาะสมในการดูดเยื่อบุโพรงมดลูกส่งตรวจทางพยาธิวิทยาของผู้ป่วยที่มาด้วยเลือดออกผิดปกติจากโพรงมดลูก ในกลุ่มวัยก่อนหมดประจำเดือน*

วัสดุและวิธีการ*: เป็นการศึกษาไปข้างหน้า ศึกษาผู้ป่วยที่มาด้วยอาการเลือดออกผิดปกติจากโพรงมดลูกในกลุ่มวัยก่อนหมดประจำเดือนที่ได้รับการดูดเยื่อบุโพรงมดลูกเพื่อส่งตรวจทางพยาธิวิทยาที่มารับบริการที่โรงพยาบาลศูนย์ราชบุรี โดยกลุ่มศึกษาทุกรายจะได้รับการบันทึกข้อมูลส่วนตัว ตรวจภายใน และตรวจ คลื่นเสียงความถี่สูงทางช่องคลอด เพื่อนำข้อมูลมาวิเคราะห์ความสัมพันธ์ของการเกิดภาวะเยื่อบุโพรงมดลูกหนาตัวผิดปกติ และมะเร็งโพรงมดลูกทางสถิติ*

ผลการศึกษา*: ผู้ป่วยที่มาด้วยเลือดออกผิดปกติจากโพรงมดลูกที่ได้รับการดูดชิ้นเนื้อในโพรงมดลูกเพื่อส่งตรวจทางพยาธิวิทยาจำนวน 200 ราย พบว่ามี 14 ราย (ร้อยละ 7) ที่พบภาวะเยื่อบุโพรงมดลูกหนาตัวผิดปกติ และพบมะเร็งโพรงมดลูก 7ราย (ร้อยละ 3.5) จากการศึกษาทางสถิติพบว่าผู้ป่วยที่มีภาวะอ้วน ผู้ที่รับประทานยา tamoxifen ความหนาของโพรงมดลูกมากกว่า 10 มิลลิเมตร มีความสัมพันธ์ต่อการเกิดภาวะเยื่อบุโพรงมดลูกหนาตัวผิดปกติ และมะเร็งโพรงมดลูกทางสถิติ ($p = 0.004, 0.041, 0.001$ ตามลำดับ) อีกทั้งยังพบว่าหากมีความเสี่ยงมากกว่า 1 ใน 3 ข้อนี้จะยิ่งเพิ่มความเสี่ยงได้สูงมากขึ้นด้วย*

สรุป*: ผู้ป่วยที่มีเลือดออกผิดปกติจากโพรงมดลูกในวัยก่อนหมดประจำเดือน ที่มีความเสี่ยงมากกว่า 1 ใน 3 ข้อนี้ (ภาวะอ้วน ผู้ที่รับประทานยา tamoxifen หรือ ผู้ที่มีความหนาของโพรงมดลูกมากกว่า 10 มิลลิเมตร) ควรได้รับการดูดเยื่อบุโพรงมดลูกเพื่อส่งตรวจทางพยาธิวิทยา*

คำสำคัญ*: เยื่อบุโพรงมดลูกหนาตัวผิดปกติ มะเร็งโพรงมดลูก ดูดเยื่อบุโพรงมดลูก เลือดออกผิดปกติจากมดลูก*

Introduction

Abnormal uterine bleeding (AUB), characterized by symptoms such as heavy menstrual flow, bleeding between periods, menometrorrhagia, and irregular cycles, is a frequent issue, affecting an estimated 14.25% of women in their reproductive years[1]. Its causes range from nonspecific dysfunctional uterine bleeding to endometrial carcinoma. Comprehensive evaluation is crucial, especially in perimenopausal patients, where the risk of endometrial carcinoma ranges from 10% to 15%[2]. Notably, AUB is the initial symptom in approximately 75% - 90% of endometrial cancer (EC) cases[3]. In postmenopausal women with AUB, the risk of EC is approximately 10%[4], but this risk decreases to under 1% if transvaginal ultrasonography indicates an endometrial thickness (ET) of less than 4 mm.[5]

For premenopausal women with AUB, however, this risk assessment is less clear due to the inconsistent predictive value of ET[6-7]. In these cases, other clinical factors, such as obesity, never having been pregnant, infertility, metabolic syndrome, tamoxifen use, and anovulation, are considered in assessing the risk of endometrial hyperplasia and endometrial cancer (EH/EC)[8-10].

In the United States, endometrial evaluation typically involves transvaginal ultrasound and endometrial sampling, often accompanied by hysteroscopy. However, there is no agreed-upon protocol regarding the optimal sequence or combination of these procedures. Establishing absolute risk estimates is key for effective guidance[11-13].

The aim of this study was to develop a model for determining when endometrial sampling is indicated, facilitating early diagnosis and treatment of EH/EC in premenopausal women experiencing AUB.

Materials and Methods

This study was a prospective cohort analysis conducted at Ratchaburi Hospital. It involved premenopausal women with AUB who underwent endometrial sampling between November 2021 and October 2022. The study's protocol received approval from Ratchaburi's Human Research Ethics Committee. Prior to participation, eligible subjects received detailed information about the study and provided their written informed consent.

Sample size calculation

To determine the sample size, we reviewed the medical records of premenopausal AUB patients at Ratchaburi Hospital. The prevalence of EH/EC was found to be 0.3. Using the formula from Bartlett et al[14] in Fig. 1. we calculated that a minimum of 150 cases was necessary. The study included peri- or premenopausal women with AUB who consented to participate. We excluded women in menopause and those with early menarche (less than 2 years), previous pelvic radiation, endometrial sampling within the last 6 months, current pregnancy, postabortion within 3 months, or systemic diseases. Women with bleeding from cervical or vaginal lesions were also excluded.

$$n = \frac{z^2_{1-\frac{\alpha}{2}}\, p(1-p)}{d^2}$$

Fig. 1. Sample size calculation.

n (sample size). P (expected prevalence or proportion). d (deviation errors = 0.05). z (statistic for a level of confidence)

Clinical evaluation

In this study, premenopausal women with AUB underwent the following clinical evaluations: (a) a pelvic examination to exclude vaginal and cervical lesions, (b) transvaginal ultrasound, conducted by a gynecological doctor, to measure ET. This was done by viewing the uterus's sagittal section to measure the endometrium line from one basalis layer to the other. The thickness was recorded in millimeters, and (c) endometrial sampling using either a Pipelle device or dilation and curettage. Samples were examined by gynecologic pathologists.

Statistical analysis

In the statistical analysis, continuous variables were presented as medians and interquartile ranges, while qualitative variables were shown as counts and percentages. Univariate logistic regression was used to analyze all independent variables, with results expressed as odds ratios (OR) and 95% confidence intervals (CIs). Multivariate logistic regression helped identify variables significantly associated with EH/EC. This analysis included variables that had a p value ≤ 0.25 in the univariate model. Categorical variable comparisons were made using the chi-square test, and relative risk was calculated to ascertain the association between one or more risk factors and EH/EC. All statistical analyses were conducted using IBM SPSS Statistics, version 23 (IBM Corp, Armonk, NY, USA), considering a p value < 0.05 as statistically significant.

Results

In this study, 200 eligible premenopausal patients with AUB underwent endometrial sampling at Ratchaburi Hospital. The majority of AUB cases occurred in women aged 41–50 years (58%). Common characteristics among these patients were obesity (27%), nulliparity (17.5%), hypertension (17%), dyslipidemia (12.5%), diabetes (9.5%), and tamoxifen use (9.5%). Transvaginal ultrasound revealed that 38% of the AUB patients had an ET thickness greater than 10 mm. Histological examination of endometrial samples identified 14 women (7%) with EH and 7 women (3.5%) with EC (Table 1).

Table 1. Baseline patient characteristics among women with abnormal uterine bleeding.

Characteristic	Study participants (n=200) Number (%)
Age(years)	
< 30	6 (3.0)
31 - 40	42 (21.0)
41 - 50	116 (58.0)
> 50	36 (18.0)
BMI ≥ 30 (kg/m^2)	54 (27.0)
Nulliparous	35 (17.5)
Type II diabetes	19 (9.5)
Hypertension	34 (17.0)
Dyslipidemia	25 (12.5)
Metabolic syndrome	6 (3.0)
Tamoxifen user	19 (9.5)
PCOS	8 (4.0)
Endometrial thickness > 10 mm.	76 (38.0)
Histology	
Endometrial cancer	7 (3.5)
Endometrial hyperplasia	14 (7.0)
Proliferative endometrium	90 (45.0)
Secretory endometrium	38 (19.0)
Endometrial polyp	51 (25.5)

BMI: body mass index, PCOS: polycystic ovarian syndrome

Univariate logistic regression analysis indicated significant associations of EH/EC with a body mass index ≥ 30 kg/m^2 (OR 20.46, 95% CI 3.04 - 137.58, p = 0.002), tamoxifen use (OR 13.04, 95% CI 1.25 - 135.88,p = 0.032), and an ET > 10 mm (OR 15.61, 95% CI 2.34 - 104.28, p = 0.005) (Table 2).

Table 2. Univariate logistic regression: factors associated with endometrial hyperplasia and endometrial cancer.

Variables	OR	95% CI	p value
BMI ≥ 30 kg/m^2	20.46	3.04 to 137.58	0.002
Nulliparous	3.50	0.49 to 24.99	0.211
Type II diabetes	0.39	0.02 to 7.36	0.533
Hypertension	1.31	0.23 to 7.58	0.760
Dyslipidemia	1.99	0.17 to 23.32	0.580
Tamoxifen user	13.04	1.25 to 135.88	0.032
PCOS	1.51	0.68 to 33.64	0.790
Endometrial thickness > 10 mm.	15.61	2.34 to 104.28	0.005

BMI: body mass index, CI: confidence intervals, EH/EC: endometrial hyperplasia/endometrial cancer, OR: odds ratio, PCOS: polycystic ovarian syndrome

Multivariate analysis using the stepwise method confirmed significant associations of EH/EC with a body mass index ≥ 30 kg/m^2 (95% CI 1.54 - 147.59, p = 0.004), tamoxifen use (95% CI 1.33 - 165.76, p = 0.041), and ET > 10 mm (95% CI 5.66 - 134.95, p = 0.001). Factors not included in the model were nulliparity, type II diabetes mellitus, hypertension, dyslipidemia, and polycystic ovary syndrome (Table 3).

Table 3. Multivariate logistic regression: predictors of endometrial hyperplasia and endometrial cancer.

Variable	95% CI		p value
	Lower	Upper	
BMI ≥ 30 kg/m^2	1.54	147.59	0.004
Tamoxifen user	1.33	165.76	0.041
Endometrial thickness > 10 mm	5.66	134.95	0.001

* Using the stepwise method, variables that not included in the model were nulliparity, type II diabetes mellitus, hypertension, dyslipidemia, and polycystic ovary syndrome.
BMI: body mass index; CI: confidence interval

The study found that having two or three risk factors was significantly more prevalent in women with EH/EC than in controls (47.62% vs 5.03% and 19.05% vs 0%, respectively, p < 0.001). There was no significant difference in EH/EC prevalence among AUB patients with only one risk factor (Table 4). The analysis did not isolate individual risk factors for EH/EC but demonstrated that patients with two or three of these risk factors were strongly associated with EH/EC.

Table 4. Comparative analysis of risk factors in women with and without endometrial hyperplasia and endometrial cancer.

Risk factors (BMI > 30 kg/m^2, tamoxifen user, endometrial thickness > 10 mm)	Women without EH/EC n (%) 179 (100)	Women with EH/EC n (%) 21 (100)
None	97 (54.19)	0 (0)
1 risk factor	73 (40.78)	7 (33.33)
2 risk factors	9 (5.03)	10 (47.62)
3 risk factors	0 (0)	4 (19.05)

BMI: body mass index, EH/EC: endometrial hyperplasia/endometrial cancer

Discussion

This study revealed that the incidence of EH/EC in premenopausal women with AUB was 10.5%, aligning closely with previous reports suggesting a prevalence of 10% to 15% in this demographic[2, 9]. Despite this, the low overall incidence of the disease suggests that frequent endometrial sampling might be excessively invasive for this group. While factors such as type II diabetes, metabolic syndrome, and nulliparity have been strongly linked to EH/EC in other studies[13,15], this correlation was not statistically significant in our research. However, consistent with prior findings[15,17-19], obesity showed a strong association with EH/EC.

For postmenopausal women experiencing initial episodes of bleeding, transvaginal ultrasound is typically the primary diagnostic test, with biopsy recommended for those showing an ET greater than 4 mm. However, in premenopausal women with AUB, such risk stratification is challenging due to inconsistent results in the predictive accuracy of ET[6-7, 12]. In our study, transvaginal ultrasound was used to measure ET, and we found that an ET greater than 10 mm was significantly associated with EH/EC. In contrast, no EH/EC cases were observed in women with an ET of 4 mm or less. This finding aligns with previous studies that included ET in their multivariate models and identified a strong correlation between an ET greater than 10 mm and EH/EC[17-19].

Current guidelines advise considering various clinical risk factors, such as age, obesity, and the use of unopposed estrogen, in the assessment of premenopausal women with AUB. However, these guidelines do not provide clear directives on how to incorporate these factors into the decision-making process for endometrial sampling[8-10, 13, 15-16].

One of the main strengths of this study is its design as a prospective cohort study, which allowed for comprehensive data collection on risk assessment, pelvic examination, and ultrasound evaluation in women with AUB who underwent endometrial sampling. Nevertheless, a notable limitation of this study was the low prevalence of EH/EC in the sample. Additionally, the study's findings were somewhat limited by the small number of participants who had type II diabetes and metabolic syndrome in the premenopausal AUB group.

Conclusion

This study identified that obesity, tamoxifen use, and an ET greater than 10 mm were significantly associated with EH/EC. Therefore, endometrial sampling is recommended for patients exhibiting more than one of these risk factors.

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Potential conflicts of interest

The author declares no conflicts of interest.

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