RESEARCH ARTICLE

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Endometrial Thickness Measurement as Predictor of Endometrial Hyperplasia and Cancer in Perimenopausal Uterine Bleeding: Cross-Sectional Study

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Abstract

Background: Endometrial thickness (ET) measurement was an alternative method for predicting abnormal endometrial pathology in postmenopausal bleeding. Cut-off value of ET measurement could not be use in perimenopausal bleeding. **Objective:** Aim of this study was to investigate appropriate ET cut-off value for perimenopause women with abnormal uterine bleeding (PEMB) and abnormal endometrial histopathology. **Material and methods:** This was a cross-sectional study. PEMB at Bhumibol Adulyadej Hospital between July 2018 and June 2022 were recruited. Subjects who met inclusion criteria underwent ET measurement and endometrial biopsy via endometrial aspirator. Participants who had histopathology report of endometrial hyperplasia and more were classified as the study group. The Control group were subjects with no endometrial hyperplasia or cancer. Demographic and clinical character data were included. Correlation of ET and endometrial histopathology were calculated for statistical significance. **Results:** A total of 304 cases were included. After exclusion, 254 subjects were recruited for this study. There were 22 and 232 cases in the study and control groups, respectively. The mean age and body mass index (BMI) of participants were 44.7 years old and 27.5 kg/m^2, respectively. Prevalence of endometrial hyperplasia and cancer in perimenopausal uterine bleeding were 7.5 (19/254) and 1.2 (3/254) percent, respectively. Endometrial thickness equal to and more than 8 mm was associated with abnormal endometrial histopathology with statistical significance. Age, BMI, nulliparity, anovulatory bleeding history, hypothyroidism, diabetes mellitus and anovulation state of both groups were comparable. **Conclusions:** Endometrial thickness equal or more than 8 mm were significantly associated with endometrial hyperplasia or more among perimenopausal women with abnormal uterine bleeding.

Keywords: Endometrial cancer- endometrial hyperplasia- endometrial thickness- perimenopause- abnormal uterine bleeding

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Introduction

Perimenopause is the transitional period from active female sexual function to the menopausal stage. During the transitional period of perimenopause to menopause, the ovaries still produced estrogen and occasionally progesterone. When the women turned into the menopausal stage, the ovaries produced minimal sex steroids (estrogen and androgen) (Taylor et al., 2020).

Menstrual cycle changes are usually the first sign of perimenopause, some women have regular cycles until menopause, some women have irregular menstrual cycles and some have irregular bleeding which could be abnormal uterine bleeding. Anovulation often occurs during perimenopause. In the anovulatory cycles there was no progesterone secretion from corpus luteum to change proliferative endometrium to secretory endometrium. In ovulatory cycle, cessation of progesterone secretion induced breakdown of endometrium tissue leading to menstruation. In anovulatory cycle, there was no progesterone secretion leading to persisting of proliferative endometrium (Taylor et al., 2020).

Perimenopausal bleeding was sometimes hard to distinguish normal from abnormal uterine bleeding (AUB). AUB was altered on interval, regularity, amount and duration of cycle (Taylor et al., 2020). Common causes of AUB in perimenopause are anovulation, fibroids, cervical and endometrial polyp and thyroid dysfunction. However, endometrial hyperplasia and cancer (EH/EC) should be concerned (Solone et al., 2020).

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Unopposed estrogen from anovulation or other causes might developed to abnormal growth namely endometrial hyperplasia. Endometrial hyperplasia was the consequence process of chronic anovulation (Taylor et al., 2020). Endometrial hyperplasia was classified according to the structure and cellular atypia namely benign endometrial hyperplasia and endometrial intraepithelial neoplasia (EIN) (Solone et al., 2020). Untreated endometrial hyperplasia can progress to endometrial cancer (Taylor et al., 2020).

Endometrial tissue study was a first-line choice for management of AUB in perimenopause and menopause (Solone et al., 2020). The tissue for the study came from fractional uterine curettage, office endometrial tissue aspiration or endometrial tissue biopsy via hysteroscopy (Taylor et al, 2020). When the endometrial tissue sampling was difficult to perform, endometrial thickness (ET) measurement via transvaginal ultrasonography was acceptable. Endometrial thickness in perimenopause still had variation for the prediction of endometrial hyperplasia and malignancy (Dowdy et al., 2020). ET less than 4 mm in menopausal women was less likely endometrial cancer (ACOG, 2018). However, there was no cut-point level of ET for perimenopausal women who had abnormal uterine bleeding (Jha et al., 2021).

The aim of this study was to investigate the correlation of abnormal endometrial histopathology in perimenopausal women with abnormal uterine bleeding and endometrial thickness.

Materials and Methods

This cross-sectional study was conducted at Department of Obstetrics and Gynecology, Bhumibol Adulyadej Hospital (BAH), Royal Thai Air Force, Bangkok, Thailand. This study was approved by BAH ethics committee in 2022 (IRB No.64/65).

Subjects were perimenopausal women who attended gynecologic clinic with AUB between July 2018 and June 2022. All cases underwent office endometrial tissue sampling and ET measurement via transvaginal ultrasonography per the department guideline protocol. Disposable plastic endometrial tissue sampler used in this study was a commercial kit (endocell®, Wallach, CT, USA). Endometrial tissue from the sampling was fixed in 10% formaldehydes solution and then sent to department of pathology. Endometrial specimens were processed and embedded in paraffin blocks. Hematoxylin and Eosin staining (H&E) were used in this study. Histopathology of the endometrial was interpreted and reported by gynecologic pathologists.

Subjects were divided into study and control groups. Study group contained subjects who had abnormal endometrial pathology, namely benign endometrial hyperplasia, EIN and endometrial cancer. Subjects who had non precancerous or cancerous endometrial pathology were placed in control group. Demographic and clinical characters of cases were retrieved from electronic medical records. Perimenopausal women were women who had consecutive amenorrhea for less than one year. According to STRAW classification in year 2010, the subjects had FSH level to define as stage -2 and -1 (Taylor et al., 2020). Inclusion criteria were perimenopausal women who had abnormal uterine bleeding (PEMB). Exclusion criteria were age below 35 years old, the lack of menstruation for over one year, pregnancy, gynecologic malignancy, hematological disease and history of antiplatelet or anticoagulant used. Data from medical records namely age, body mass index (BMI), parity, endometrial histopathology reports, ET, bleeding pattern, anovulation status, hypothyroidism and diabetes mellitus were collected.

Demographic characters were presented as descriptive statistic. Continuous variables were presented as mean and standard deviation. Categorical variables were presented as number (percent), Chi-square or Fisher's exact test with appropriated condition. Statistical program in this study was International Business Machines Statistical Package for the Social Sciences statistics version 28 (SPSS, IBM Corp, NY, USA). Univariate and multivariate logistic regression were calculated with statistically significant factor from Chi-square or Fisher's exact test. Receiver operating curve (ROC) was generated between the significant factor and histopathology for the optimal cut-off point. Statistical significance was defined as p-value less than 0.05.

Results

During period of study, 304 cases of PEMB were recruited. A total of 254 cases were included in this study as shown in Figure 1. Study and control groups consisted of 22 and 232 cases, respectively. There were 17, 2 and 3 cases of benign endometrial hyperplasia, EIN and endometrial cancer, respectively. The mean age of participants were 44.7 years old. Two third of cases (156/254) had BMI equal or more than 25 kg/m^2. Prevalence of EH/EC in PEMB were 7.5 (19/254) and 1.2 (3/254) percent, respectively. One-fifth of cases (53/254) were nulliparity. Percentage of nulliparity among study and control group were 40.9 (9/22) and 19 (44/232), respectively with statistical significance. Other demographic characters in both groups were comparable.

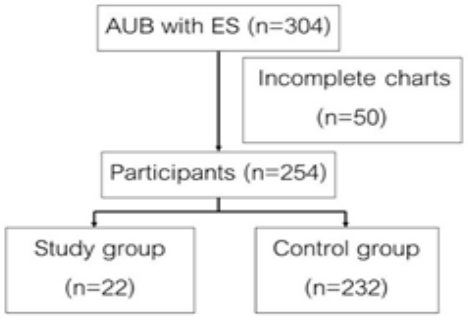

Figure 1. Flow Chart of Study. AUB, abnormal uterine bleeding; ES, endometrial sampling; Study group, subjects who had abnormal endometrial pathology namely benign endometrial hyperplasia, endometrial intraepithelial neoplasia (EIN) and endometrial cancer; Control group, subjects who had xxxxxx: subjects who had non precancerous or cancerous endometrial pathology

Table 1. Demographic Characters of Study (n=22) and Control (n=232) Groups

	Study, n (%)	Control, n (%)	p-value
BMI (kg/m^2)			0.012*
< 25	3 (13.6)	95 (40.9)	
≥ 25	19 (86.4)	137 (59.1)	
Age (years) *	45.6 ± 4.9	44.7 ± 5.7	0.56
ET (mm) *	10.9 ± 4.7	8.1 ± 5.8	0.003*
Anovulatory bleeding	9 (40.9)	141 (60.8)	0.07
Nulliparity	9 (40.9)	44 (19)	0.015*
Hypothyroidism	0 (0)	5 (2.2)	0.487
DM	1 (4.5)	9 (3.9)	0.878
Anovulation	3 (13.6)	15 (6.5)	0.21

*mean ± standard deviation (SD); BMI, body mass index; ET, endometrial thickness; DM, diabetes mellitus; Study group, subjects who had abnormal endometrial pathology namely benign endometrial hyperplasia, endometrial intraepithelial neoplasia (EIN) and endometrial; cancer, control group, subjects who having non precancerous or cancerous endometrial pathology

ET of the study group was higher than that of the control group with statistical significance as shown in Table 1.

Univariate logistic regression analysis of dependent factor among study and control groups were calculated. BMI, ET and nulliparity were significant factors to EH/EC. From multivariate logistic regression analysis, only ET was the independent factor for EH/EC as presented in Table 2.

From Figure 2, correlation between BMI and EH/EC were generated to find out diagnostic power. Area under the ROC curve was 0.618 that indicated an inappropriateness for a cut-off point. ET and EH/EC were generated by ROC. Area under the curve of a 8 mm ET was 0.702 that gave sensitivity, specificity, positive predict value (PPV) and negative predictive value (NPV) at 78.6, 61.6, 13.2 and 97.5 percent, respectively as shown in Figure 3.

ET equal to and more than 8 mm was associated with EH/EC with statistical significance.

Discussion

AUB causes the physiological problem that leads the perimenopause women to visit physicians. Most common cause of AUB in perimenopause reported by Taylor's work was benign condition (atrophic endometrium and endometrial polyp) ranging from 86 to 99 percent. However, EH/EC occurrence was between 1 and 14 percent in perimenopause (Taylor et al., 2020).

In the present study, EH/EC was reported at 9.7 (22/254) percent. From previous literatures, prevalence of EH/EC were reported ranging from 4 to 15.7 percent (Sattanakho et al., 2020; Jha et al., 2021; Dhakwa et al., 2021; Soja et al., 2020; Kumari et al., 2022). Our prevalence of EH/EC was within the range of previous works above. The prevalence of endometrial cancer in the current

Table 2. Univariate and Multivariate Logistic Regression Analysis of Dependent Factor to Abnormal Endometrial Pathology

	Crude RR (95%CI)	p-value	Adjusted RR (95%CI)	p-value
BMI (kg/m^2)				
< 25	Reference	1	Reference	1
≥ 25	4.39 (1.26, 15.26)	0.02*	3.17 (0.62, 16.04)	0.164
Age (years)	1.02 (0.94, 1.11)	0.566	1.05 (0.94, 1.18)	0.369
ET (mm)				
< 8	Reference	1	Reference	1
≥ 8	5.88 (1.59, 21.77)	0.008*	6.27 (1.53, 25.71)	0.011*
Anovulatory bleeding				
No	Reference	1	Reference	1
Yes	0.45 (0.18, 1.09)	0.076	0.42 (0.12, 1.46)	0.173
Nulliparity				
No	Reference	1	Reference	1
Yes	2.96 (1.19, 7.36)	0.02*	2.69 (0.7, 10.37)	0.151
Hypothyroidism				
No	Reference	1	Reference	1
Yes	0 (0, 1)	0.999	0 (0, 1)	0.999
DM				
No	Reference	1	Reference	1
Yes	1.18 (0.14, 9.77)	0.878	2.06 (0.17, 25.32)	0.572
Anovulation				
No	Reference	1	Reference	1
Yes	2.28 (0.61, 8.6)	0.222	1.17 (0.11, 12.23)	0.894

abnormal endometrial pathology, abnormal endometrial pathology namely benign endometrial hyperplasia, endometrial intraepithelial neoplasia (EIN) and endometrial cancer; BMI, body mass index; ET, endometrial thickness; DM, diabetes mellitus

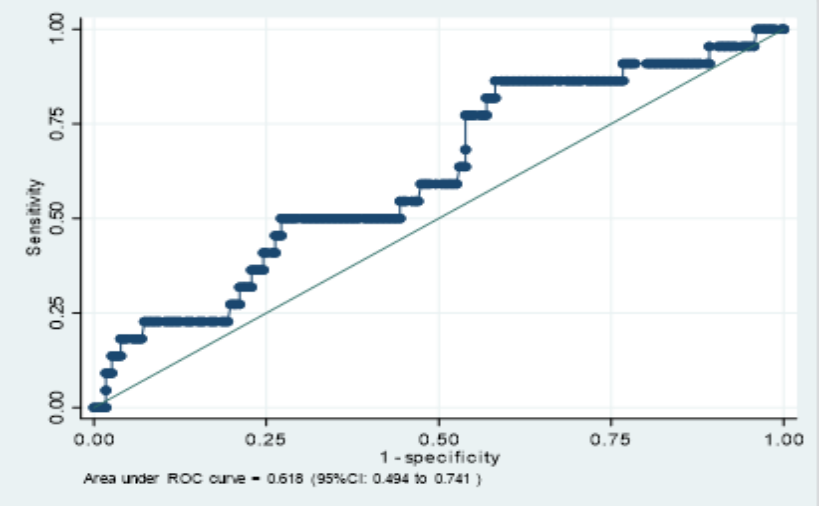

Figure 2. ROC of BMI and Abnormal Endometrial Histopathology. ROC, receiver operating curve; BMI, body mass index(kg/m^2); abnormal histopathology, endometrial hyperplasia and cancer

study was low (3/254). Benign endometrial hyperplasia and EIN presented a 3 - 8 % risk of endometrial cancer development per year (Doherty et al., 2020). The ruling out of precancerous and malignancy condition should be concerned in PEMB (Taylor et al., 2020). Regarding to cancer concern, all subjects with abnormal uterine bleeding underwent invasive procedure for obtaining endometrial specimens. Non-invasive procedure that having good accuracy should be considered.

Sattanakho et al reported from Northeast Thailand in year 2020 that prevalence of EH/EC among perimenopause was only 4 percent (Sattanakho et al., 2020). Jha et al., (2021) reporting the prevalence of EH/EC from India and Nepal were 4.6 and 6.2 percent, respectively (Dhakwa

Table 3. Comparison Outcome of Endometrial Hyperplasia and Cancer in Women with Abnormal Uterine Bleeding from Various Study

Authors	Bar-on	Tumrongkunagon	Soja	Sattanakho	Jha	Dhakhwa	Kashyap	Kumari	Present
Years	2018	2019	2020	2020	2021	2021	2021	2022	2022
Country	Israel	Thailand	Poland	Thailand	India	Nepal	India	India	Thailand
Designs	Retro	RCT	Retro	Descriptive	Retro	Descriptive	CC	Cross	Cross
Procedure	Hys	EA/F&C					Hys	MVA	EA
Status	Peri/Meno	Peri/Meno	Peri	Peri	Peri	Peri	Peri/Meno	Peri	Peri
N	405	85	298	557	1,084	96	80	70	254
Age*	54.1	46.9					50.7		44.7
BMI*	23.5						26.3		27.5
Nulliparity**				0 (0)	99 (9.1)				54 (20.8)
Anovulatory **				87 (15.6)	143 (13.1)				150 (59)
Hypothyroidism**					57 (5.2)				5 (1.96)
DM**									10 (3.93)
Anovulation**									18 (7)
ET (mm)*		9.2	12.7		9.4		12.6		8.3
POH**	16(4.8)	5.9	13.4	3.3	2.8	6.2	17.5	10 (14.3)	19 (7.5)
POC**	14(4.2)	7	1	0.7	1.8	0	10	1 (1.4)	3 (1.2)
Sensitivity	46.7							76	78.6
Specificity	90							68.9	61.6
PPV	31.1							57.6	13.2
NPV	94.6							83.8	97.5

*mean, ** n (%), N, total cases; BMI, body mass index (kg/m^2); anovulatory, anovulatory bleeding; DM, diabetes mellitus; ET, endometrial thickness; POH, prevalence of benign endometrial hyperplasia and endometrial intraepithelial neoplasia (EIN); POC, prevalence of endometrial cancer; PPV, positive predictive value; NPV, negative predictive value; RCT, randomized controlled trial; Retro, retrospective; CC, case control; cross-sectional study; EA, endometrial aspiration; F&C, fractional curettage; D&C, dilatational curettage; Hys, hysteroscopic biopsy; MVA, manual vacuum aspiration by Karman's canula; Peri, perimenopause; Meno, menopause

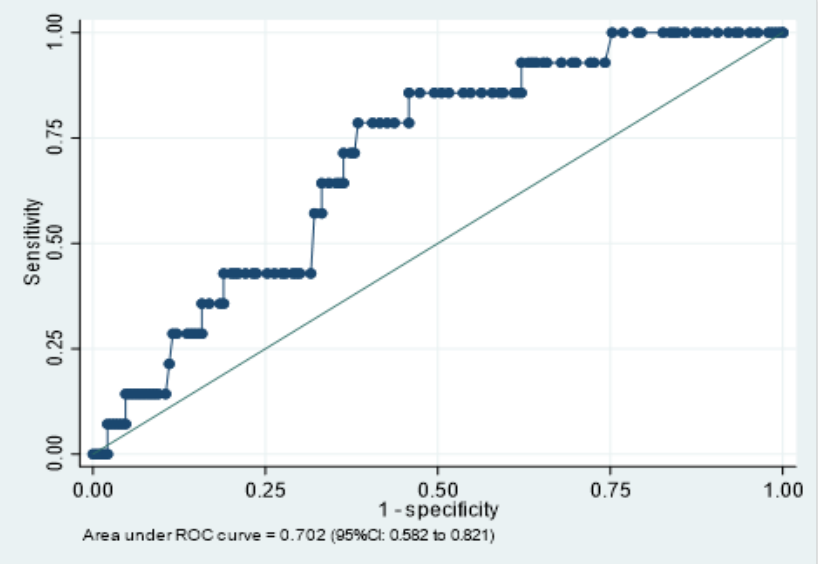

Figure 3. ROC of ET and Abnormal Endometrial Histopathology. ROC, receiver operating curve; ET, endometrial thickness; abnormal histopathology, endometrial hyperplasia and cancer

et al., 2021). One-third (186/557) of Sattanakho's, half (532/1084) of Jha's and two-third (156/254) of current study had BMI more than 25 kg/m^2 (Sattanakho et al., 2020; Jha et al., 2021). Prevalence of EH/EC of Soja's and Kumari's population from Poland and India were 14.4 and 15.7 percent, respectively (Soja et al., 2020; Kumari et al., 2022). Twenty-one (15/70) of Kumari's population had BMI more than 30 kg/m^2 (Kumari et al., 2022). Estrone was produced by adipose tissue. It could stimulate endometrium resulting in unopposed estrogen endometrium in perimenopause and menopause women. Women with high BMI was associated of high percentage of body fat (Taylor et al., 2020).

From current study, mean age of participants in current study were 44.7 years old. According from ACOG, endometrial tissue was recommended to perform in women who had age more than 45 years old with AUB (Dowdy et al., 2020). However, the BMI of the subjects in the current study has no association with EH/EC. Wise et al., (2016) reported that PEMB with BMI more than 30 kg/m^2 had higher risk of endometrial cancer development 4 times than those with lesser BMI (95% CI 1.36 - 11.74). Guraslan et al., (2016) reported from Turkiye that PEMB with BMI more than 30 kg/m^2 had 6.6 times higher risk for EH/EC than those with BMI lesser than 30 kg/m^2 (95% CI 2.4 - 17.9). Wise et al., (2016) and Guraslan et al., (2016) revealed that PEMB with BMI more than 30 kg/m^2 had higher risk of EH/EC. However, mean BMI of perimenopausal population of the current study was only 27.5 kg/m^2. Jayasinghe et al., (2019) reported from New Zealand that half of women with age between 16 and 45 years old had BMI more than 25 kg/m^2. Santas et al., (2018) from Turkiye reported that one-quarter of women with age between 15 and 49 years old had BMI more than 30 kg/m^2. Diet and life style of women in Turkiye and New Zealand might be differed from the current study. Both Turkiye and New Zealand people commonly consumed dairy products and sweety foods. This might be the reason why BMI is not associated with EH/EC.

Another study from India in year 2016. Jha reported that PEMB who had BMI of more than 25 kg/m^2 had 4.4 times higher risk for EH/EC than their peers (95% CI 1.51 - 14.36). Age and BMI of Jha and current study looked similar. Heavy menstrual bleeding of Jha and the current study were 86.9 (941/1084) and 40.9 (104/254) percent, respectively (Jha et al., 2021). The pattern of bleeding in Jha and current study were different. Etiology of EH/EC were multifactorial factors (Dowdy et al., 2020).

From current study, Patients with ET of more than 8 mm had 6.27 times higher risk for EH/EC than others (95% CI 1.53 - 25.7). According to 2018 ACOG recommendation, menopausal women who had AUB with ET of more than 4 mm should underwent endometrial tissue study. However, there was no ET consensus in PEMB (ACOG, 2018). Patients with ET more than 13 mm and 10.5 mm had high risk of EH/EC at 22.6 and 2.58 times, respectively (Jha et al., 2021; Kumari et al., 2022). From the current study, ET 8 mm cut off was less than those in Jha et al., (2021) and Kumari et al., (2022)'s reports. Another report from Sattanakho et al., (2020) of Thailand revealed that patients with ET of more than 8 mm had 1.39 times higher risk for EH/EC (95% CI 0.48 – 4.54). However, Patients with ET of more than 8 mm in Sattanakho did not show statistical significance. The different of the current and Sattanakho et al., (2020) results might come from the difference of cases character. Two-third (371/557) of cases in Sattanakho's et al., (2020) study had BMI less than 25 kg/m^2. Three quarter (422/557) of Sattanakho's subjects had parity equal and more than two. Multiparity and low BMI were the protective factor of EH/EC development (Taylor et al., 2020). In summary, subjects in Sattnakho's et al., (2020) report had lower prevalence of EH/EC (4 percent) than the current study (9.7 percent) that might be from multiparity and low BMI.

The ET cut point in the current study was further calculated for diagnostic power. ET of more than 8 mm gave sensitivity, specificity, PPV and NPV at 78.6, 61.6, 13.2 and 97.5 percent, respectively. ET of more than

10.5 and 13 mm from Kumari's and Jha's literatures had sensitivity, specificity, PPV and NPV at percentage of 89.5/88.2, 86.3/98, 70.68/76.3 and 95.7/99.4, respectively (Kumari et al., 2022; Jha et al., 2021). Sensitivity from the current study was lower than those from Kumari et al., (2022)'s and Jha et al., (2021)'s reports. However, NPV of the current result was in lieu with Kumari et al., (2022)'s and Jha et al., (2021)'s. Even though, our sensitivity was not as high as those of Kumari et al., (2022)'s and Jha et al., (2021)'s, NPV was the value of concern. If the patient's ET was less than 8 mm, it indicated that probability of negative for EH/EC was 97.5 percent. If we use the cut point as the ACOG recommendation at 4 mm, nearly all cases of PEMB would undergo endometrial tissue study for histopathology (ACOG, 2018). The higher ET cut point value, the lower NPV would be the result. The lower ET cut point that gives appropriate sensitivity and high NPV should be considered. In era of minimal invasive concept, PEMB and ET of less than 8 mm should receive counseling that she had low risk of EH/EC (3/118).

ET measurement in the current study was in grey scale ultrasonography. Power doppler mode was suggest by Batra et al., (2022); Veena et al., (2018) and Bar-on et al., (2018). The diagnostic power of power doppler of Bar-on et al., (2018) was presented in Table 3. The ET measurement by grey scale ultrasonography in the current study had similar result with Batra et al., (2022)'s;Veena et al., (2018)'s and Bar-on et al., (2018)'s study.

Strength of this study was the large number of perimenopausal women who had abnormal uterine bleeding and underwent both ET measurement and histopathology. The limitation of study was its retrospective design. Unavailing confounding factor from retrospective design was the limitation of this study.

In conclusion, Perimenopause women with abnormal uterine bleeding should be informed that endometrial tissue sampling was a gold standard for definitive diagnosis. If endometrial tissue sampling were difficult or painful, serial endometrial thickness measurement was an alternative option.

Author Contribution Statement

All authors contributed equally in this study.

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