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# Contributing factors related to abnormal uterine bleeding in perimenopausal women: a case–control study

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## Abstract

Abnormal uterine bleeding (AUB) during the menopausal transition results in reproductive endocrine disorders and both physiological and pathological changes, substantially impacting women's health. This study aimed to investigate the factors influencing AUB in perimenopausal women. Between April 2021 and June 2022, 120 perimenopausal women with AUB in the menopausal transition, diagnosed and treated at the Gynaecology Department of Kunming Tongren Hospital, were included in the case group. Concurrently, women undergoing routine health examinations at the same hospital were randomly selected as the control group. Univariate and multivariate logistic regression analyses identified factors related to AUB. The univariate analysis revealed significant associations ( $P < 0.05$ ) between AUB and several factors, including age, body mass index (BMI), age at menarche, gravidity, and intrauterine device (IUD) placement in perimenopausal women. The multivariate regression analysis indicated that the independent risk factors for AUB include benign endometrial lesions (odds ratio [OR] 5.243, 95% confidence interval [CI] 3.082–9.458,  $P < 0.001$ ), endometrial thickness  $\geq 10$  mm (OR 1.573, 95% CI 0.984–3.287,  $P < 0.001$ ), age  $\geq 50$  years (OR 2.045, 95% CI 1.035–4.762,  $P = 0.001$ ), BMI  $\geq 25$  kg/m<sup>2</sup> (OR 2.436, 95% CI 1.43–4.86,  $P = 0.002$ ), and IUD placement (OR 2.458, 95% CI 1.253–4.406,  $P < 0.001$ ). Abnormal uterine bleeding during the menopausal transition is associated with several factors, including age, BMI, and IUD placement, highlighting the importance of early screening for these risk factors in the diagnosis and treatment of AUB.

**Keywords** Abnormal uterine bleeding, Diagnosis, Influencing factors, Perimenopause, Treatment

## Introduction

The menopausal transition, a crucial phase in the progression from puberty to the end of reproductive life, substantially impacts middle-aged women's lives. This transition typically begins around the age of 40 and occurs mainly between 41 and 55 years. During this period, 75–80% of women experience various physical and psychological symptoms, including abnormal uterine bleeding (AUB) and perimenopausal syndrome [1, 2]. Abnormal uterine bleeding is characterised by abnormal menstrual vaginal bleeding, extended menstrual flow, or abnormally increased menstrual flow. Numerous causes of AUB in perimenopausal women have been identified, such as intrauterine polyps (AUB-P), adenomyosis

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(AUB-A), and uterine leiomyoma (AUB-L). Notably, patients may suffer from one or more diseases causing or relating to AUB [3, 4].

Abnormal uterine bleeding has become a prevalent gynaecological issue. A 2001 survey in China found an AUB incidence of 34.5% among 9,951 women patients [5], and approximately 25% of women in the United States have undergone gynaecological surgery for this condition [6]. Menopausal transition AUB often lacks distinctive early symptoms, leading to frequent misdiagnosis or oversight. If untreated, AUB can lead to complications such as anaemia, infection, and even the risk of malignant transformation into endometrial carcinoma (EC) [7]. Abnormal uterine bleeding substantially affects women's physical and mental health, impacting their quality of life and potentially endangering their lives. Therefore, investigating the factors influencing AUB is crucial for future prevention and carcinogenesis management.

Early, accurate examination and diagnosis are key to improving early diagnosis rates and timely, effective treatment in postmenopausal women with AUB [8]. Although the substantial impact of AUB on women's health and quality of life is recognised, there is a knowledge gap regarding specific risk factors and early diagnostic methods. Current endometrial pathology diagnoses rely on non-invasive imaging modalities, such as sonography, computed tomography, and magnetic resonance imaging, and invasive procedures, such as blind biopsy and hysteroscopy [9]. However, these methods often only detect already abnormal diseased tissue and are limited in the early identification of individuals at high risk of developing AUB.

Consequently, this study investigates the various factors contributing to AUB during this pivotal phase. The study aims to assist clinicians in identifying high-risk factors for AUB during the menopausal transition, facilitating early diagnosis and effective treatment. Ultimately, this research may contribute to extending patients' life expectancy, enhancing their quality of life, and promoting more effective disease management.

## Materials and methods

### Related definitions

The following criteria define abnormal uterine bleeding: ① a menstrual cycle length of < 21 days or > 35 days, with a bleeding duration exceeding 8–10 days; ② menstrual blood loss exceeding 80 ml per menstrual cycle, or a subjective feeling of excessive menstrual flow (some studies consider the soaking of six sanitary pads or tampons in a single day as abnormal); and ③ the presence of intermenstrual bleeding [10]. Since 2011, the International Federation of Gynecology and Obstetrics has classified the underlying causes of AUB into a system known as

PALM–COEIN. Under PALM classification, various aetiologies involve structural modifications that can be identified using imaging methodologies or histopathological assessments. These include AUB-P, AUB-A, AUB-L (also referred to as fibroids), endometrial malignancies, and endometrial hyperplasia with atypia. On the other hand, the COEIN category encompasses conditions in which structural changes within the uterus are absent, including coagulopathy, ovulatory dysfunction, endometrial-related factors, iatrogenic influences, and unclassified causes. Additionally, within this classification, AUB-Ls are further subcategorised based on their location, being classified as either submucosal or situated in other areas [3].

Natural menopause is marked by the cessation of menstruation for a duration of 12 months and typically occurs between the ages of 49 and 52. However, the timing of menopause varies across different ethnic groups, with a median age of 51.4 years observed in high-income nations [11]. Perimenopause refers to the transitional phase in midlife that precedes the end of reproductive capability in women. Currently, over 850 million women worldwide are aged between 40 and 60 years, with 88% experiencing a perimenopausal transition. This transition typically occurs at an average age of 51.4 years, following a Gaussian distribution ranging from 40 to 58 years [12]. Premenopause is a relative term denoting the absence of symptoms associated with perimenopause or menopause.

### Research participants

This study involved 120 women undergoing menopausal transition and experiencing AUB. These participants, diagnosed and treated in the Department of Gynaecology at Kunming Tongren Hospital between April 2021 and June 2022, formed the case group. These women presented with varying degrees of menstrual cycle disorders, prolonged menstruation, increased menstrual flow, or mild anaemia. The inclusion criteria for this group included the following: ① aged between 41 and 55 years (menopausal transition period) [1]; ② exhibiting clinical manifestations of AUB; ③ having a definite pathological diagnosis; and ④ possessing complete case data. The exclusion criteria included the following: ① aged < 41 or > 55 years; ② bleeding from the cervix, external vagina, or urethra; ③ pregnancy; ④ coagulation disorders; ⑤ severe liver disease; ⑥ presence of other reproductive system tumours; and ⑦ incomplete patient data.

The control group comprised another 120 healthy women who underwent physical examinations at the same hospital during the same period. The inclusion criteria for the control group included the following: ① aged between 41 and 55 years (menopausal transition period); and ② absence of AUB. The exclusion criteria

included the following: ① presence of systemic diseases; ② presence of medical diseases; and ③ incomplete data. All participants were informed about the study and provided signed informed consent. A flowchart illustrating the entire process of this study is presented in Fig. 1.

The required sample size (N) for the study was calculated using logistic regression according to the following formula:

$$N = \frac{Z_{1-\alpha/2}^2 * p(1 - p)}{d^2}$$

Here, the event occurrence (p) refers to the incidence of AUB [5, 6], set at 0.30 (30%). The significance level (α) was established at 0.05, with  $Z_{1-\alpha/2}$  being the Z-score corresponding to the chosen significance level (α/2). For α=0.05,  $Z_{1-\alpha/2}$  is approximately 1.96. Effect sizes (d) typically range from small to medium, estimated between 0.2 and 0.5; here, we set d=0.20. Based on these parameters, approximately 20 samples were required for subsequent analysis. Having 120 samples in each group (case and control) ensured that the statistical requirements for this study were met.

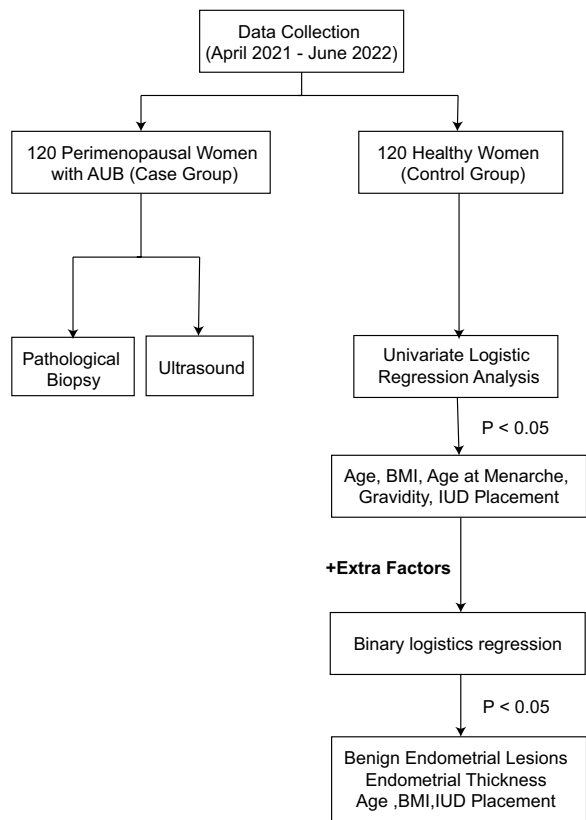


Fig. 1 A flowchart covering the whole process of this work

### Investigation methods

An investigation team was established, comprising the attending physician and a data collector. Printed survey questionnaires were distributed for face-to-face investigations. The survey included the following general clinical data: ① age; ② BMI; ③ age at menarche; ④ gravidity; ⑤ parity; ⑥ number of miscarriages; ⑦ whether an IUD was inserted; ⑧ whether menopause was delayed; ⑨ medical history, including hypertension, diabetes, hyperlipidaemia, thyroid disease, use of oestrogen drugs, and genital tract inflammatory diseases; and ⑩ family history. The classification of obesity in Asian women is BMI ≥ 25 kg/m<sup>2</sup> [13–15].

### Examination method

After a gynaecological examination, procedures such as colour Doppler ultrasonography, hysteroscopy, and pathological biopsy of endometrial curettage were performed.

- ① Ultrasonography: This modality objectively reflects the size and shape of the uterus, endometrial thickness, endometrial echo, and endometrial blood flow signal, aiding in the identification of uterine and adnexal lesions. A colour Doppler ultrasound diagnostic instrument (MyLab™ 30Gold, Italy Esaote Medical Equipment Co.), with a CA1421 probe type and a probe frequency of 2.0–6.0 MHz, was employed. The operation was transabdominal. Image acquisition and data measurement were conducted by different physicians to ensure repeatability between the observers.
- ② Hysteroscopy: As a newer examination method, hysteroscopy has gained increasing favour among clinicians for its advantages of direct visibility and clear vision. It allows for a clear view of the internal structure of the entire uterine cavity, facilitating the selection of lesions under direct vision for biopsy. This is conducive to diagnosing various endometrial lesions, such as AUB-P, submucosal endometrial fibroids, and EC.
- ③ Endometrial pathological examination: Pathological biopsy of endometrial tissue taken by diagnostic curettage or hysteroscopy is the gold standard for the diagnosis of AUB.

The pathological changes of the endometrium were classified according to the World Health Organization's 1994 classification. Endometrial hyperplasia is divided into four groups based on glandular complexity and nuclear atypia: non-atypical endometrial hyperplasia (simple, complex) and atypical endometrial hyperplasia (simple, complex) [16].

### Statistical analysis

This study used SPSS 26.0 software (IBM Corp, Chicago, IL, USA) for the statistical analysis. The normality of the quantitative data was assessed using the Kolmogorov–Smirnov test (test level:  $P=0.05$ ). Quantitative data conforming to a normal distribution were presented as means  $\pm$  standard deviations ( $\bar{x} \pm s$ ). An independent sample t-test was employed for comparisons between the groups. Data not normally distributed were expressed as the median (25th–75th percentile) and compared using the Mann–Whitney U test. Qualitative data were presented as n (%). The  $\chi^2$  test was chosen if the total number of cases was  $>40$  and the theoretical frequency was  $>5$ ; otherwise, Fisher's exact probability test was uniformly selected. Important factors, as determined by univariate analysis results and professional knowledge, were included. Binary logistic regression was used for the multivariate analysis to calculate the odds ratio (OR) and regression coefficient of each risk factor. A  $P$ -value of  $<0.05$  was considered statistically significant. Variable assignments for the logistic regression analysis were as follows: ① pathological outcomes: '1' = normal endometrium; '2' = benign changes of the endometrium, '3' = EC or precancerous lesion; ② endometrial thickness: '1' = endometrial thickness  $\leq 10$  mm, '2' = endometrial thickness  $\geq 10$  mm; ③ endometrial echo: '1' = uniform, '2' = non-uniform; ④ age: '1' =  $<50$  years, '2' =  $>50$  years; ⑤ BMI: '1' =  $<25$  kg/m<sup>2</sup>, '2' =  $>25$  kg/m<sup>2</sup>; ⑥ age at menarche: '1' =  $<12$  years, '2' =  $>12$  years; ⑦ gravidity: '1' =  $<1$  time, '2' =  $>1$  time; ⑧ IUD placement: '1' = 'Yes', '2' = 'No'; and ⑨ history: '1' = 'Yes', '2' = 'No'.

## Results

### Comparison of pathological biopsy results between the two groups

The difference in the pathological biopsy results of the endometrium between the two groups was statistically

significant ( $P<0.001$ ). The proportion of benign endometrial changes (68.3% vs. 9.2%) and cancer or precancerous changes (6.7% vs. 0.8%) was considerably higher in the case group compared with the control group, as detailed in Table 1 and illustrated in Fig. 2.

### Comparison of ultrasound findings between the two groups

The ultrasonography results of the case group were compared with those of the control group, focusing on endometrial thickness and endometrial echo. In line with the International Endometrial Tumor Analysis statement [17], the highest measurement in the sagittal plane for each patient, encompassing both endometrial layers (double endometrial thickness), was recorded as the endometrial thickness value. The proportion of women with an endometrial thickness of  $>10$  mm was markedly higher in the case group than in the control group, with a statistically significant difference (72.5% vs. 15%,  $P<0.001$ ). Similarly, the proportion of women with heterogeneous endometrial echogenicity was significantly higher in the case group than in the control group (55% vs. 20%,  $P<0.001$ ). These findings are shown in Table 1 and Fig. 3.

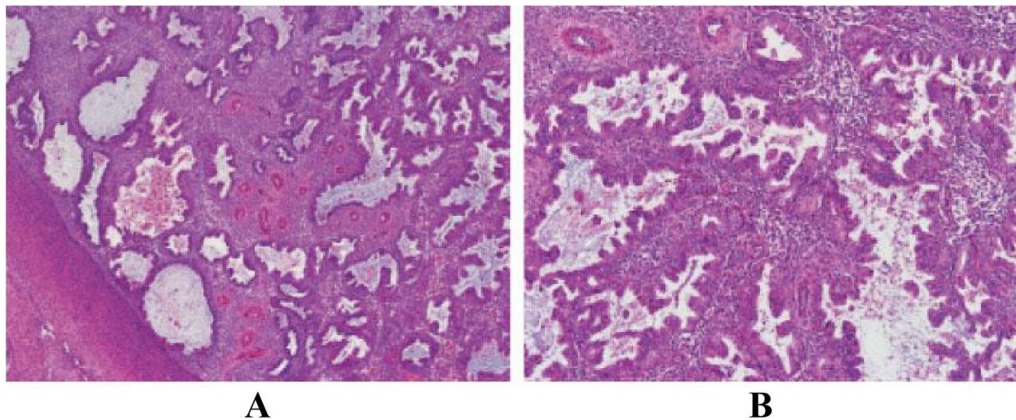
### Independent risk factors for abnormal uterine bleeding in perimenopausal women determined by univariate analysis

Univariate analysis revealed several notable differences between the case and control groups. The proportion of women aged  $>50$  years was higher in the case group (34.2% vs. 20%,  $P=0.014$ ). There were 37 obese women (BMI  $\geq 25$ ) in the case group, significantly more than in the control group (30.8% vs. 15.8%,  $P=0.006$ ). The proportion of women aged  $<12$  years at menarche in the case group was significantly higher than in the control group (15% vs. 5.8%,  $P=0.020$ ). The proportion of women with a gravidity of  $>1$

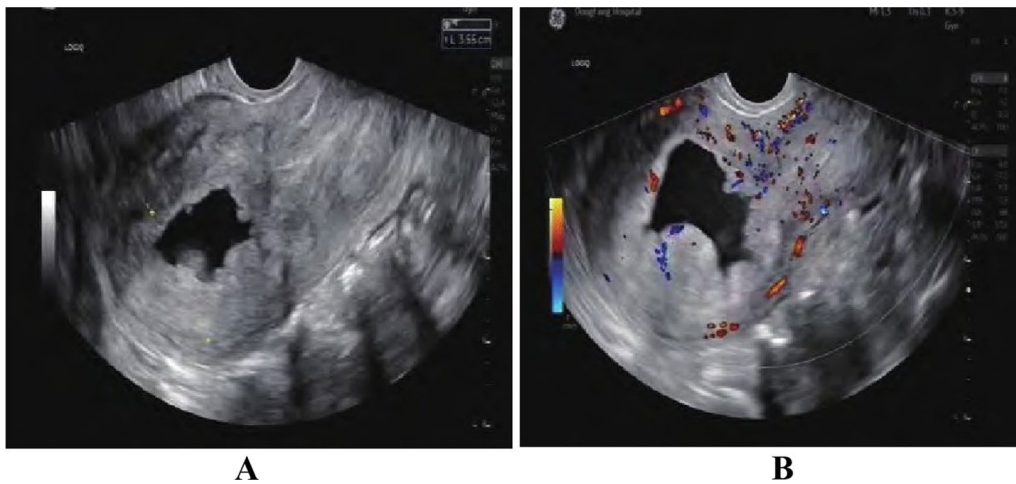
**Table 1** Comparison of pathological results and ultrasonic examination results between two groups

| Indicators                                   | Case group (n = 120) | Control group (n = 120) | $\chi^2$ | P        |
|--|----------------------|-------------------------|----------|----------|
| Pathological results                         |                      |                         | 103.736  | $<0.001$ |
| Normal endometrial                           | 30 (25.0)            | 108 (90.0)              |          |          |
| Benign changes of endometrium                | 82 (68.3)            | 11 (9.2)                |          |          |
| Endometrial carcinoma or precancerous lesion | 8 (6.7)              | 1 (0.8)                 |          |          |
| Endometrial thickness (mm)                   |                      |                         | 80.610   | $<0.001$ |
| $<10$  | 33 (27.5)            | 102 (85.0)              |          |          |
| $\geq 10$                                    | 87 (72.5)            | 18 (15.0)               |          |          |
| Endometrial echo                             |                      |                         | 31.360   | $<0.001$ |
| Uniform                                      | 54 (45.0)            | 96 (80.0)               |          |          |
| Non-uniform                                  | 66 (55.0)            | 24 (20.0)               |          |          |





**Fig. 2** Pathological light microscopic features of endometriosis. **A** composed of hyperplastic endometrial glands and mesenchymal cells (HE×40); **B** glands with complex hyperplasia and secretory changes (HE×100)



**Fig. 3** Imaging picture of a patient with endometrial cancer on transvaginal colour Doppler ultrasound. The patient was a female, 49 years old, with clinical presentation of irregular vaginal bleeding. The endometrial echogenicity was observed in 2D colour Doppler ultrasound, which showed that the endometrial echogenicity was heterogeneous and chaotic, with irregular endometrial morphology and contour, blurred echogenicity of the baseline, and unclear demarcation with the local myometrium, see **A**. Colour Doppler blood flow imaging showed rich blood flow signals, and the diagnosis of endometrial cancer was made, see **B**

time in the case group was higher than that in the control group (65% vs. 35.8%,  $P < 0.001$ ). Additionally, the proportion of IUD placement in the case group was significantly higher than that in the control group (76.7% vs. 63.3%,  $P = 0.024$ ). No significant differences were found in terms of parity, the number of miscarriages, delayed menopause, medical history, and family history between the two groups ( $P > 0.05$ ), as presented in Table 2.

#### Independent risk factors for abnormal uterine bleeding in perimenopausal women determined by multivariate logistics regression analysis

Binary logistic regression was employed to incorporate factors with  $P < 0.05$  from the results of the univariate analysis, as well as factors professionally considered to influence AUB, such as medical history, as independent variables. Abnormal uterine bleeding was utilised

**Table 2** Single factor analysis of AUB in menopausal transition women

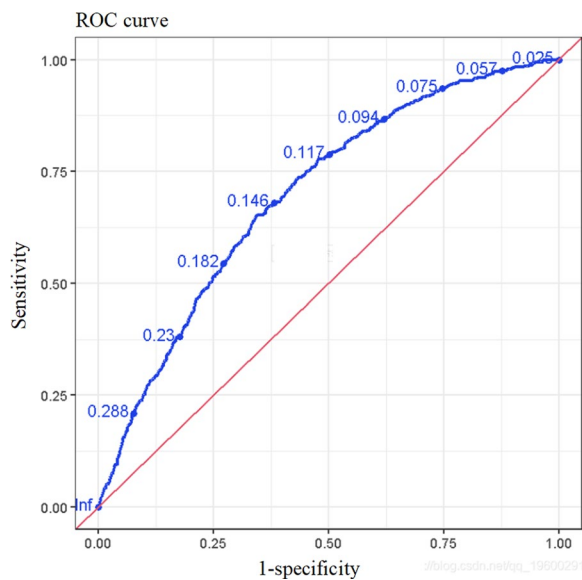
|                          | Case group (n = 120) | Control group (n = 120) | t/x <sup>2</sup> | P       |
|--------------------------|----------------------|-------------------------|------------------|---------|
| Age (year)               |                      |                         | 6.098            | 0.014   |
| < 50                     | 79 (65.8)            | 96 (80.0)               |                  |         |
| ≥ 50                     | 41 (34.2)            | 24 (20.0)               |                  |         |
| BMI (kg/m <sup>2</sup> ) |                      |                         | 7.547            | 0.006   |
| < 25                     | 83 (69.2)            | 101 (84.2)              |                  |         |
| ≥ 25                     | 37 (30.8)            | 19 (15.8)               |                  |         |
| Age at menarche (year)   |                      |                         | 5.403            | 0.020   |
| ≤ 12                     | 18 (15.0)            | 7 (5.8)                 |                  |         |
| > 12                     | 102 (85.0)           | 113 (94.2)              |                  |         |
| Gravidity (time)         |                      |                         | 20.418           | < 0.001 |
| ≤ 1                      | 42 (35.0)            | 77 (64.2)               |                  |         |
| > 1                      | 78 (65.0)            | 43 (35.8)               |                  |         |
| Parity (time)            | 1.695 ± 0.543        | 1.326 ± 0.652           |                  | 0.819   |
| Abortion (time)          | 0.431 ± 1.062        | 0.283 ± 0.945           |                  | 0.073   |
| IUD placement            |                      |                         | 5.079            | 0.024   |
| Yes                      | 92 (76.7)            | 76 (63.3)               |                  |         |
| No                       | 28 (23.3)            | 44 (36.7)               |                  |         |
| Menopause delayed        |                      |                         | 0.603            | 0.438   |
| Yes                      | 59 (49.2)            | 53 (44.2)               |                  |         |
| No                       | 61 (50.8)            | 67 (55.8)               |                  |         |
| Past history             |                      |                         | 1.068            | 0.301   |
| Yes                      | 62 (51.7)            | 54 (45.0)               |                  |         |
| No                       | 58 (48.3)            | 66 (55.0)               |                  |         |
| Family history           |                      |                         | 2.017            | 0.156   |
| Yes                      | 2 (1.7)              | 0 (0.0)                 |                  |         |
| No                       | 118 (98.3)           | 120 (100.0)             |                  |         |

as the dependent variable, and stepwise regression was applied to identify relevant factors. To ensure the retention of explanatory variables in the model, the inclusion level was set at 0.10, and the exclusion level was set at 0.15.

The logistic regression analysis results are presented in Table 3. Benign endometrial lesions (OR 5.243, 95% confidence interval [CI]: 3.082–9.458,  $P < 0.001$ ), endometrial thickness  $\geq 10$  mm (OR 1.573, 95% CI 0.984–3.287,  $P < 0.001$ ), age  $\geq 50$  years (OR 2.045, 95% CI 1.035–4.762,

**Table 3** Multivariate logistic regression analysis results of AUB in menopausal transition women

| Variable  | $\beta$ | SE    | Wald test | P        | OR    | 95% CI      |             |
|---|---------|-------|-----------|----------|-------|-------------|-------------|
|   |         |       |           |          |       | Upper Limit | Lower Limit |
| Pathologic outcomes (Benign changes of endometrium) | 1.834   | 0.286 | 24.495    | < 0.001* | 5.243 | 3.082       | 9.458       |
| Endometrial thickness ( $\geq 10$ )                 | 0.852   | 0.365 | 6.463     | < 0.001* | 1.573 | 0.984       | 3.287       |
| Endometrial echo (Non-uniform)                      | 0.273   | 0.158 | 2.974     | 0.436    | 1.035 | 0.652       | 2.476       |
| Age ( $\geq 50$ )                                   | 0.825   | 0.342 | 5.361     | 0.001*   | 2.045 | 1.035       | 4.762       |
| BMI ( $\geq 25$ kg/m <sup>2</sup> )                 | 0.983   | 0.375 | 7.082     | 0.002*   | 2.436 | 1.143       | 4.986       |
| Age at menarche ( $\leq 12$ year)                   | -0.531  | 0.584 | 0.993     | 0.426    | 0.357 | 0.105       | 1.367       |
| Gravidity ( $\leq 1$ time)                          | -0.324  | 0.487 | 0.521     | 0.382    | 0.735 | 0.281       | 1.843       |
| IUD placement (No)                                  | 0.980   | 0.304 | 10.485    | < 0.001* | 2.458 | 1.253       | 4.406       |
| Past history (No)                                   | -0.593  | 0.524 | 1.438     | 0.350    | 0.645 | 0.284       | 1.525       |



**Fig. 4** The ROC curve based on the multivariate logistic regression analysis

$P=0.001$ ),  $\text{BMI} \geq 25 \text{ kg/m}^2$  (OR 2.436, 95% CI 1.143–4.986,  $P=0.002$ ), and IUD placement (OR 2.458, 95% CI 1.253–4.406,  $P<0.001$ ) were identified as independent risk factors for AUB in perimenopausal women. The ROC analysis result is shown in Fig. 4.

## Discussion

Excessive menstrual bleeding, known as menorrhagia, has emerged as a prevalent manifestation of AUB in perimenopausal women. Alongside vaginal bleeding, other symptoms such as pallor, pelvic discomfort, and fatigue are frequently encountered. The duration of bleeding and the volume of blood loss prior to hospital admission are notably higher in perimenopausal individuals compared with their postmenopausal counterparts. Factors including age, menstrual characteristics, and diabetes heighten the susceptibility to endometrial cancer in women experiencing postmenopausal bleeding [18].

The results of this study indicated that the incidence of benign endometrial changes, cancer, or precancerous changes in women in the case group was notably higher than that in the control group. This suggests that benign endometrial changes or carcinogenesis are the primary causes of AUB. Moreover, due to dysfunction of the hypothalamic-pituitary-ovarian axis in perimenopausal women, the timing, amount, and ratio of oestrogen and progesterone production affecting the endometrium become imbalanced, leading to endometrial simple or complex hyperplasia [19]. Consequently, clinical practice should pay attention to physiological changes during the menopausal transition in women, and appropriate

oestrogen supplementation to maintain certain physiological functions of the genital tract is beneficial in preventing infection.

In this study, colour Doppler ultrasound was employed to measure endometrial thickness and endometrial echogenicity. This technique allows for the visual detection of uterine size, intrauterine structure, the relationship of the endometrial lining, and blood flow distribution, offering the advantages of being non-invasive, allowing dynamic monitoring, and being repeatable [20]. The uterine artery Doppler indices, including resistance index, pulsatility index, and peak systolic velocity, exhibited substantially lower values in the malignant group than in the benign group. Endometrial thickness was found to be a reliable indicator for the diagnosis of endometrial cancer, achieving an area under the curve value of 0.89. For women with postmenopausal bleeding, a threshold value of 12.5 mm provided the highest levels of sensitivity and specificity [21]. The study also found that the proportion of women with endometrial thickness of  $>10 \text{ mm}$  was notably higher in the case group than in the control group, and the proportion of heterogeneous endometrial echogenicity was also higher. The potential reasons for this include the tendency of the endometrium in patients with AUB to show infiltrative growth, with benign changes or precancerous changes being more likely. Consequently, when lesions appear, they invade the endometrial myometrium and serosa, resulting in uneven endometrial echoes and unclear demarcation between the endometrium and myometrium [22]. It is suggested that colour Doppler ultrasonography can serve as a simple and effective tool for screening high-risk AUB groups in clinical practice by measuring endometrial thickness and echogenicity in the early evaluation of patients with AUB, offering substantial clinical application value.

The results of this study demonstrated that benign endometrial lesions, endometrial thickness  $\geq 10 \text{ mm}$ , age  $\geq 50$  years,  $\text{BMI} \geq 25 \text{ kg/m}^2$ , and IUD placement are independent risk factors for AUB in perimenopausal women. These findings align with those reported by Xiao et al. [23], who identified IUD placement and obesity as risk factors for AUB in this demographic. A potential explanation for these results is that endometrial fibrinolytic activity increases following IUD placement, particularly in the early stages, when fibrinolytic activity is at its peak, leading to enhanced menstrual flow. Affected by IUDs, the endometrium augments prostaglandin production through its secretory effect, thereby increasing capillary permeability and fragility, resulting in a greater volume of menstrual blood [24]. Additionally, prolonged retention of the upper contraceptive ring in the uterine cavity may lead to inflammatory reactions and other forms of bleeding. Thus, it is advisable

for perimenopausal women to remove the contraceptive device promptly to prevent postmenopausal bleeding and infection.

AUB may be an expression of hormonal milieu, or it could be the clinical presentation of benign or malignant lesions of female genital tract in perimenopausal woman. This study suggested that benign endometrial lesions was related to the risk for AUB in perimenopausal women. In line with our finding, Talukdar et al. [25] found that histopathology of endometrium in patients with AUB was predominantly simple typical type and that the majority of cases were diagnosed as fibroid uterus. Moreover, another study [26] demonstrated that structural causes of AUB were identified in 81.3% of cases, with adenomyosis (33.65%), concomitant adenomyosis and leiomyoma (31.5%), and leiomyoma (14.8%) being the most common. The present study also evinced that endometrial thickness  $\geq 10$  mm was an independent risk factor for AUB in perimenopausal women. Indeed, consistent with this result, a previous study [27] has showed that majority of women with AUB in perimenopausal age had endometrial thickness of 10–12 mm (35.7%) followed by 7–9 mm (27.1%). Getpook et al. [28] concluded that endometrial thickness of 8 mm or less was less likely to be associated with malignant pathologies in premenopausal uterine bleeding. These findings indicated the significance of ultrasonography in measuring endometrial thickness and identifying organic causes in order to screen perimenopausal women at high risk for AUB.

Moreover, compared with women in other age groups, perimenopausal women tend to have a more stable lifestyle, better dietary conditions, lower activity levels, and more rest time. These factors, among others, contribute to the prevalence of menopausal transition obesity [29]. In this study, the proportion of obese women in the case group was considerably higher than in the control group, indicating that obesity is a risk factor for AUB. This condition may be attributed to the conversion of excessive androgens in the adipose tissue of obese women into estrone via aromatisation, leading to endometrial hyperplasia [30]. Therefore, managing body weight in perimenopausal women is crucial. Furthermore, this study underscores the importance of addressing obesity in clinical practice, as it facilitates the early detection and diagnosis of AUB in perimenopausal women.

Identifying and understanding the primary risk factors for AUB is crucial for the prevention and early detection of AUB in perimenopausal women. Investigating these influencing factors can assist healthcare professionals in identifying potential risks for AUB at an early stage. This facilitates the implementation of appropriate monitoring, examination, and intervention measures, thereby aiding in early intervention. Such steps enhance treatment

success rates, reduce disease progression, and mitigate adverse outcomes. Consequently, the findings of this study are pivotal for improving the health of women in the perimenopausal period and providing essential guidance for clinical practice.

This study has several limitations. First, the study was conducted as a single-centre study in one hospital, which might limit the generalisability of the findings to a broader population. Second, the relatively short time-frame of the study, spanning between April 2021 and June 2022, may have influenced the comprehensiveness of the results. Furthermore, the study might not have accounted for all potential confounding variables that could affect the relationship between risk factors and AUB, and there may be additional clinical influences yet to be identified. It is also important to note that haemoglobin levels and uterine size are crucial indicators in assessing the nature of AUB. A related study observed a higher incidence of moderate to severe anaemia in perimenopausal women compared with that in postmenopausal women, and substantial differences in uterine size were noted between benign and malignant groups [31]. However, due to logistical constraints, collecting relevant data was not feasible in the current study. Future multicentre, large-sample studies that incorporate a wider range of potential influencing factors for AUB may help overcome these limitations.

## Conclusion

This study suggests that AUB in perimenopausal women may be influenced by several factors, such as benign endometrial lesions, an endometrial thickness of  $>10$  mm, an age of  $>50$  years, a BMI of  $>25$  kg/m<sup>2</sup>, and IUD placement. Early recognition of these potential influencing factors could provide crucial insights into the prevention of AUB in perimenopausal women.

## Acknowledgements

We would like to express our gratitude to all those who helped us during the writing of this manuscript.

## Author contributions

TY and TJH conceived of the study, WL collates the study information, and BB and ZYC participated in its design and coordination and TY helped to draft the manuscript. All authors read and approved the final manuscript.

## Funding

None.

## Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

## Declarations

### Ethical approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Kunming Tongren Hospital on March



20, 2021. All participants signed an informed consent form for inclusion in the study.

#### Consent for publication

Not applicable.

#### Competing interests

The authors declare no competing interests.

Received: 8 December 2023 Accepted: 19 March 2024

Published online: 18 April 2024

#### References

- Lu W, Guo W, Hou K, Zhao H, Shi L, Dong K, et al. Grey matter differences associated with age and sex hormone levels between premenopausal and perimenopausal women: a voxel-based morphometry study. *J Neuroendocrinol*. 2018;30(12): e12655. <https://doi.org/10.1111/jne.12655>.
- Madhra M, Fraser IS, Munro MG, Critchley HO. Abnormal uterine bleeding: advantages of formal classification to patients, clinicians and researchers. *Acta Obstet Gynecol Scand*. 2014;93(7):619–25. <https://doi.org/10.1111/aogs.12390>.
- Munro MG, Critchley HO, Broder MS, Fraser IS, FIGO Working Group on Menstrual Disorders. FIGO classification system (PALM-COIN) for causes of abnormal uterine bleeding in nonpregnant women of reproductive age. *Int J Gynaecol Obstet*. 2011;113(1):3–13. doi: <https://doi.org/10.1016/j.ijgo.2010.11.011>.
- Zhang YW. FIGO new classification system for abnormal uterine bleeding (AUB) in non-pregnant women of childbearing age. The 10th National Obstetrics and Gynecology Academic Conference of Chinese Medical Association Gynecological Endocrine Conference (Gynecological Endocrinology Group, Menopause Group, Family Planning Group) Paper Compilation. [uncertain publisher]; 2012.
- Zhou FR, Liu X, Liu XJ, Chen ZX, Zhang R, Shen F, et al. Epidemiological study on common gynecological diseases among married women in Shandong Province. *Chin J Nat Med*. 2003;04:213–6.
- Albers JR, Hull SK, Wesley RM. Abnormal uterine bleeding. *Am Fam Phys*. 2004;69(8):1915–26.
- Pennant ME, Mehta R, Moody P, Hackett G, Prentice A, Sharp SJ, et al. Premenopausal abnormal uterine bleeding and risk of endometrial cancer. *BJOG*. 2017;124(3):404–11. <https://doi.org/10.1111/1471-0528.14385>.
- Guan SG. Clinical analysis and pathological results of uterine bleeding for 508 cases for perimenopausal women. *China Pract Med*. 2014;9(1):21–2.
- Nguyen PN, Nguyen VT. Additional value of Doppler ultrasound to B-mode ultrasound in assessing for uterine intracavitary pathologies among perimenopausal and postmenopausal bleeding women: a multicentre prospective observational study in Vietnam. *J Ultrasound*. 2023;26(2):459–69. <https://doi.org/10.1007/s40477-022-00732-w>.
- Chou B, Bienstock JL, Satin AJ. *Johns Hopkins Manual of Gynecology and Obstetrics*; 2020:6e.
- Zhu D, Chung HF, Dobson AJ, Pandeya N, Giles GG, Bruinsma F, et al. Age at natural menopause and risk of incident cardiovascular disease: a pooled analysis of individual patient data. *Lancet Public Health*. 2019;4(11):e553–64. [https://doi.org/10.1016/S2468-2667\(19\)30155-0](https://doi.org/10.1016/S2468-2667(19)30155-0).
- Brinton RD, Yao J, Yin F, Mack WJ, Cadenas E. Perimenopause as a neurological transition state. *Nat Rev Endocrinol*. 2015;11(7):393–405. <https://doi.org/10.1038/nrendo.2015.82>.
- Zhang L, Peng XT, Wang S, Sang XH, Li SH, Liu J. Comparison of diagnostic criteria for overweight and obesity among Rural Uyghur perimenopausal women in Moyu county of Xinjiang. *J Xinjiang Med Univ*. 2016;39(08):953–7.
- WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet*. 2004;363(9403):157–63. [https://doi.org/10.1016/S0140-6736\(03\)15268-3](https://doi.org/10.1016/S0140-6736(03)15268-3).
- Daida Y, Pedula K. Prevalence of overweight and obese prepregnancy BMI and excessive gestational weight gain using asian-specific cutoffs among Asian and mixed-Asian women living in Hawaii: a retrospective cohort study. *Matern Child Health J*. 2023;27(4):728–36. <https://doi.org/10.1007/s10995-022-03560-w>.
- Sobczuk K, Sobczuk A. New classification system of endometrial hyperplasia WHO 2014 and its clinical implications. *Prz Menopauzalny*. 2017;16(3):107–11. <https://doi.org/10.5114/pm.2017.70589>.
- Leone FP, Timmerman D, Bourne T, Valentin L, Epstein E, Goldstein SR, et al. Terms, definitions and measurements to describe the sonographic features of the endometrium and intrauterine lesions: a consensus opinion from the International Endometrial Tumor Analysis (IETA) group. *Ultrasound Obstet Gynecol*. 2010;35(1):103–12. <https://doi.org/10.1002/uog.7487>.
- Nguyen PN, Nguyen VT. Evaluating clinical features in intracavitary uterine pathologies among vietnamese women presenting with Peri-and postmenopausal bleeding: a bicentric observational descriptive analysis. *J Midlife Health*. 2022;13(3):225–32. [https://doi.org/10.4103/jmh.jmh\\_81\\_22](https://doi.org/10.4103/jmh.jmh_81_22).
- Yapura MJ, Zwiefelhofer EM, Pierson RA, Adams GP. Aromatase inhibitors: a new approach for controlling ovarian function in cattle. *Theriogenology*. 2018;112:18–25. <https://doi.org/10.1016/j.theriogenology.2017.08.025>.
- Patel V, Wilkinson EJ, Chamala S, Lu X, Castagno J, Rush D. Endometrial thickness as measured by transvaginal ultrasound and the corresponding histopathologic diagnosis in women with postmenopausal bleeding. *Int J Gynecol Pathol*. 2017;36(4):348–55. <https://doi.org/10.1097/PGP.0000000000000344>.
- Nguyen PN, Nguyen VT. Endometrial thickness and uterine artery Doppler parameters as soft markers for prediction of endometrial cancer in postmenopausal bleeding women: a cross-sectional study at tertiary referral hospitals from Vietnam. *Obstet Gynecol Sci*. 2022;65(5):430–40. <https://doi.org/10.5468/ogs.22053>.
- Zarbo G, Caruso G, Caruso S, Mangano U, Zarbo R. Endometrial cancer: pre-operative evaluation of myometrial infiltration magnetic resonance imaging versus transvaginal ultrasonography. *Eur J Gynaecol Oncol*. 2000;21(1):95–7.
- Xiao HL, Fan JM, Hu YG. Clinical analysis of perimenopausal abnormal uterine bleeding. *J Med Theory Pract*. 2016;29(14):1920–1. <https://doi.org/10.19381/j.jssn.1001-7585.2016.14.056>.
- Xue W, Sun AJ. Mechanism of action of sex hormones in perimenopausal abnormal uterine bleeding. *Chin J Pract Gynecol Obstet*. 2012;28(10):742–4.
- Talukdar B, Mahela S. Abnormal uterine bleeding in perimenopausal women: correlation with sonographic findings and histopathological examination of hysterectomy specimens. *J Midlife Health*. 2016;7(2):73–7. <https://doi.org/10.4103/0976-7800.185336>.
- Sah S, Dungal G, Jha M. Correlation of endometrial thickness by transvaginal sonography with histopathological examination in abnormal uterine bleeding in perimenopausal age group. *J Nepal Health Res Council*. 2023;21(1):110–4. <https://doi.org/10.33314/jnhrcv21i1.4597>.
- Sahu HD, Varma AV, Karmarkar S, Malukani K, Khanuja A, Kesharwani P. Endometrial histopathology in abnormal uterine bleeding and its relation with thyroid profile and endometrial thickness. *Cureus*. 2023;15(4): e37931. <https://doi.org/10.7759/cureus.37931>.
- Getpook C, Wattanakumtornkul S. Endometrial thickness screening in premenopausal women with abnormal uterine bleeding. *J Obstet Gynaecol Res*. 2006;32(6):588–92. <https://doi.org/10.1111/j.1447-0756.2006.00455.x>.
- Sweet MG, Schmidt-Dalton TA, Weiss PM, Madsen KP. Evaluation and management of abnormal uterine bleeding in premenopausal women. *Am Fam Physician*. 2012;85(1):35–43.
- van Weelden WJ, Fasmer KE, Tangen IL, Int'Hout J, Abbink K, van Herwaarden AE, et al. Impact of body mass index and fat distribution on sex steroid levels in endometrial carcinoma: a retrospective study. *BMC Cancer*. 2019;19(1):547. <https://doi.org/10.1186/s12885-019-5770-6>.
- Nguyen PN, Nguyen VT. Assessment of paraclinical characteristics in peri- and postmenopausal bleeding women: is there a correlation between hemoglobin levels and ultrasonic indices? *J Taibah Univ Med Sci*. 2022;18(3):488–98. <https://doi.org/10.1016/j.jtumed.2022.10.011>.

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