Original Article

Clinical Predictors of Endometrial Hyperplasia in Premenopausal Women with Abnormal Uterine Bleeding

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Abstract

Background: Abnormal uterine bleeding (AUB) is common prior to menopause, and the risk of endometrial hyperplasia is highly variable. Knowing which predictors can be easily obtained may help in stratifying the risk for clinically indicated endometrial assessment. **Objectives:** To determine the prevalence and the histopathological spectrum of EH in premenopausal women with AUB in Babylon Province and to identify independent clinical and sonographic predictor(s) of histologically confirmed EH. **Materials and Methods:** The study was a prospective analytical cross-sectional study conducted in Babylon Province, Iraq, during January to June 2026, which involved 320 women of reproductive age (18–49 years) with AUB undergoing clinically indicated endometrial sampling. Before histopathology, demographic, reproductive, metabolic, bleeding related and transvaginal ultrasonographic variables were recorded. The main outcome was endometrial hyperplasia without atypia and atypical hyperplasia/endometrial intraepithelial neoplasia (EIN); carcinoma was reported separately. Logistic regression and receiver operating characteristic (ROC) analysis were performed, using bootstrap internal validation. **Results:** Hyperplasia without atypia was found in 50 women (15.6%), atypical hyperplasia/EIN in 18 (5.6%) and carcinoma in 7 (2.2%). In the primary analysis (excluding carcinoma) of 313 women, 68 (21.7%) were found to have hyperplasia. Independent predictors were age (adjusted odds ratio [aOR] per year, 1.08; 95% confidence interval [CI], 1.03–1.13), body mass index (BMI; aOR per kg/m², 1.10; 95% CI, 1.04–1.17), polycystic ovary syndrome (PCOS; aOR, 2.31; 95% CI, 1.15–4.64), diabetes mellitus (aOR, 2.48; 95% CI, 1.14–5.39), chronic anovulation (aOR, 2.57; 95% CI, 1.27–5.21), and endometrial thickness (aOR per mm, 1.29; 95% CI, 1.18–1.41). The combined model had an apparent area under the ROC curve (AUC) of 0.871 and a bootstrap-corrected AUC of 0.858; calibration was acceptable. **Conclusions:** Age, BMI, PCOS, diabetes, chronic anovulation and endometrial thickness were able to identify premenopausal women with AUB with increased probability of histologically confirmed endometrial hyperplasia.

Keywords: Abnormal uterine bleeding, Body mass index, Endometrial thickness, Endometrial hyperplasia, Prediction model, Polycystic ovary syndrome

Introduction

One of the most common gynecological complaints of women of reproductive age is abnormal uterine bleeding (AUB) which can significantly cause chronic blood loss, iron-deficiency anemia, lack of energy and psychosocial dysfunction, and have a significant impact on physical health, fertility, work productivity, and quality of life. The International Federation of Gynecology and Obstetrics (FIGO) has standardized the terminology of AUB based on bleeding frequency, regularity, duration and volume, and has introduced PALM–COEIN classification of underlying causes of AUB which includes polyp, adenomyosis, leiomyoma, malignancy/ hyper-plasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic and not otherwise classified [1-4]. While this schema helps to streamline the organization of endometrial samp-

ling, an important clinical issue is determining which women who are premenopausal should undergo endometrial sampling to exclude significant disease and prevent unnecessary invasive procedures in women at low risk [5,6,7]. Endometrial Hyperplasia (EH) is the abnormal growth of endometrial glands which is most often caused by estrogenic stimulation for too long a period without an adequate level of progesterone. Currently, there are two classifications: Hyperplasia without atypia and atypical hyperplasia/endometrial intraepithelial neoplasia (EIN), which is a precursor lesion for progression to and coexistence with endometrioid carcinoma [8-13]. Thus, effective tissue sampling and pathological diagnosis are still needed, but there is inter-observer variability in diagnosing borderline and atypical lesions, which is best addressed by expert review, where clinically appropriate [14,15]. However, the absolute risk of endometrial cancer or atypical hyperplasia in unselected premenopausal women with AUB is relatively low and selective rather than routine biopsy is suggested [6,16]. Risk-based evaluation is biologically warranted since unopposed estrogen is a main component to endometrial proliferation. Chronic anovulation, obesity, insulin resistance, diabetes mellitus, PCOS and infertility can cause a prolonged exposure to estrogen with a decreased exposure to protective progesterone [12,17,18]. BMI is another potential predictor as obesity also leads to peripheral estrogen production, a reduction in sex hormone-binding globulin and also promotes hyperinsulinemia and chronic inflammation. Insulin resistance and growth signaling can further be affected by diabetes to have an impact on the process of endometrial proliferation [19]. Likewise, PCOS is characterized by chronic oligo-anovulation, metabolic abnormalities and is linked to an elevated risk of EH and endometrial cancer especially in women with persistent amenorrhea, weight gain, diabetes mellitus and/or prolonged endometrial thickening [20,21]. With that being said, age is also important, but current guidelines focus on how age is considered in the context of ongoing AUB, ineffective medical management, and metabolic and anovulatory risk factors [1,7]. Transvaginal ultrasonography (TVUS) is a popular technique in the assessment of AUB as it allows identification of structural abnormalities and information on endometrial thickness (ET). However, unlike postmenopausal women, ET fluctuates naturally across the menstrual cycle and is dependent on the ovulatory status, PCOS, hormonal therapies and the method of measurement; thus, no universally reliable threshold exists in premenopausal women [22-24]. Other sonographic features such as endometrial echogenicity, irregularity, cystic changes and vascular patterns standardized using International Endometrial Tumor Analysis (IETA) terminology could give complementary diagnostic information [25]. Given these restrictions, there has been a growing interest in predicting with multiple variables. Several risk scores, nomograms, and prediction models have shown combinations of obesity, diabetes, ET, bleeding characteristics, PCOS and other clinical and sonographic variables to be superior to single variables in predicting outcomes [26-29]. Population differences, indication for biopsy, outcome definition and prevalence of disease may, however, restrict transportability of the models. Prediction models should be controlled for model complexity, assessed for discrimination and calibration, internally validated (preferably using bootstrap methods) and ultimately evaluated for clinical utility and external validity [30,31]. In view of the still scarce evidence from Middle Eastern populations, the present study was designed to determine the prevalence and the histopa-

thological spectrum of EH in premenopausal women with AUB in Babylon Province and to identify independent clinical and sonographic predictor(s) of histologically confirmed EH. It also sought to evaluate the predictive ability of each of the variables and to create an internally validated parsimonious multivariable prediction model. We hypothesized that age, BMI, PCOS, diabetes mellitus, chronic anovulation, duration of AUB and increased endometrial thickness would be associated with EH and that all of these together would be able to discriminate better than any individual.

Materials and Methods

Study setting and reporting

A prospective analytical cross-sectional study was carried out in gynecology outpatients and diagnostic hysteroscopy and in-patient services of Babylon Maternity and Children Teaching Hospital and Imam Al-Sadiq Teaching Hospital in addition to some private gynecology clinics in Hilla city, Babylon Province, Iraq from January 1 to June 30, 2026. Histopathological examination was carried out in special laboratories for histopathology in Hilla that are certified. The same criteria for eligibility, data-collection form, ultrasound protocol, and rules for tissue classification were used at each of the sites. Reporting was done following STROBE and elements for prediction-models were informed by TRIPOD.

Participants and sampling

Women who were premenopausal (aged 18–49 years) and who were having AUB were invited to participate if they were undergoing an endometrial biopsy for clinically indicated reasons, hysteroscopy-guided sampling or dilatation and curettage. Premenopausal status was defined as a patient who still had menses or showed evidence that she had not gone through menopause. No invasive procedure was done for research purposes only.

Eligibility criteria

For inclusion, AUB had to be available, as well as sufficient baseline clinical and ultrasonographic data, a sufficient histopathological specimen and consent. The exclusion criteria included pregnancy or pregnancy related bleeding, menopause, previous diagnosis or treatment of endometrial hyperplasia, previous diagnosis of endometrial carcinoma prior to enrolment, previous hysterectomy, active genital tract malignancy, inadequate tissue and missing primary outcome data. The use of hormonal contraception or progestogen was not automatically excluded, but rather recorded.

Sample size

A sample size of 320 women was chosen to estimate a frequency of hyperplasia around 20%, and give around 60–70 events of the outcome for a model with six predictors in an economical manner. There were pre-specified degrees of freedom for the models to prevent overfitting and bootstrap internal validation was planned.

The clinical and reproductive assessment was performed following method

Age, place of residence, smoking, age at menarche, gravidity, parity, nulliparity, infertility, miscarriages, menstrual regularity, oligomernorrhea, amenorrhea, use of hormonal treatment, intrauterine device, diabetes, hypertension, thyroid disease, dyslipidaemia and family history of the disease were collected by trained clinicians. PCOS was documented based on accepted clinical criteria and not just self-report. Chronic anovulation was diagnosed in women with persistent oligomenorrhea/amenorrhea with clinical evidence of ovulatory dysfunction and no major alternative causes of amenorrhea.

Anthropometric and metabolic assessment

Weight and height were obtained using calibrated equipment, in light clothes and without shoes. BMI in kg/m² was kept continuously for primary modelling and conventional categories were used descriptively. Diabetes was determined by presence of a diagnosis in the medical record, treatment with glucose-lowering medications, or laboratory diagnosis. Similarly, hypertension and thyroid diseases were confirmed from the clinical records.

The assessment of abnormal uterine bleeding is outlined

Bleeding was defined according to the FIGO terms. Heavy menstrual bleeding, irregular bleeding, intermenstrual bleeding, frequent bleeding, prolonged bleeding, infrequent bleeding followed by excessive bleeding and mixed patterns were the main patterns. The exact time (in months) was kept and then divided into <3, 3–6, and >6 months for descriptive purposes. Hemoglobin was used as a routine assessment to determine anemia.

Transvaginal ultrasonography

When clinically appropriate, transvaginal ultrasonography was done prior to histopathology. The endometrial thickness was measured in the midsagittal plane, as the thickest double layer without taking into account the presence of intracavitary fluid. If Cycle Day was known then this was recorded. The appearance of the endometrium (homogeneous/ heterogeneous), cystic spaces, focal polyp, presence of leiomyoma, adenomyosis and ovarian morphology compatible with PCOS were noted. Hyperplasia was not used as the diagnostic reference that was used for sonography.

Endometrial sampling and histopathology

Samples were collected using Pipelle biopsy, hysteroscopy-guided biopsy or dilatation and curettage, as clinically indicated. Specimens were fixed in buffered formalin, routinely processed and assessed by pathologists blinded to the prediction analysis. Diagnoses were classified as proliferative endometrium, secretory endometrium, disordered proliferative endometrium, polyp, hyperplasia without atypia, atypical hyperplasia/EIN, carcinoma or others. All EIN/carcinoma diagnoses were reviewed on the same samples by a second pathologist, and a random 10% of other specimens were reviewed by the same pathologist who made the initial diagnosis, and any discrepancies settled by consensus.

Outcomes and predictors

The main outcome was when the hyperplasia was confirmed by histology without atypia, or atypical hyperplasia/EIN. Carcinoma cases were reported separately and not included in the primary binary analysis as the title and primary question was about hyperplasia. Clinical relevance dictated the prespecification of candidate predictors: age, BMI, PCOS, diabetes, chronic anovulation and endometrial thickness. Secondary predictors (including event-count constraints) included: nulliparity; infertility; duration of AUB; heterogeneous/cystic endometrium; hormonal use.

Statistical analysis

Normally distributed variables are reported as mean ± standard deviation, skewed variables as median (interquartile range [IQR]) and categorical variables as n (%). t test, Mann–Whitney U test, chi-square test or Fisher exact test was used to compare the hyperplasia and non-hyperplasia groups. Crude odds ratios (ORs) were calculated by univariable logistic regression. A multivariable model comprised six prespecified predictors, which were not categorized. Restricted cubic splines were used to check linearity in the logit, variance inflation

factors were used to check for collinearity, and standardized residuals to check for influential observations. AUC and 95% CI were used to quantify discrimination. Youden index was used for descriptive purposes as cutoffs for individual continuous variables. The calibration intercept/slope, Brier score, and Hosmer–Lemeshow test were used to assess the calibration. The estimation of optimism was performed by taking 1000 bootstrap resamples. Predictor missingness was <10% and multiple imputation by chained equations was planned but the primary outcome was not imputed. Two-sided $p<0.05$ was considered significant. R version 4.4 or SPSS version 29 was used for analyses.

Ethical approval

Ethical and scientific clearance was given by the relevant institutional research ethics committee and administrative clearance by the hospitals involved prior to recruitment. Written informed consent was given. Endometrial sampling was only done for clinical indications, as judged by the gynecologist treating the woman, and never for research purposes only. Identifiers have been coded and securely stored. Women with a diagnosis of Hyperplasia, EIN and Carcinoma were immediately referred for specialist management as per institutional pathways.

Indications for sampling and verification of eligibility

Persisting or recurring AUB, age-related risk, failure of medical treatment, chronic anovulation, PCOS with prolonged amenorrhea, obesity or diabetes, and infertility with irregular bleeding, were clinically indicated for endometrial sampling as was suspicious endometrial appearance or other concern documented by the treating gynecologist. Details of indication, method of sampling, menstrual-cycle day (when known), hormonal exposure and previous treatment were noted prior to pathology. Clinically and testing (when indicated) excluded pregnancy. The number of participants excluded from the primary analysis is reported in the participant flow because of inadequate specimens.

The standardization and quality control of ultrasound

A harmonized acquisition sheet was used by trained operators to obtain a transvaginal ultrasound prior to tissue sampling. The thickness of the endometrium was determined in the midsagittal plane in the thickest double-layer region without including any fluid within the uterine cavity, and separately for the focal lesions. The following variables were recorded: cycle phase, bleeding at examination, hormonal treatment, uterine lesions, endometrial heterogeneity, cystic spaces, vascularity and image adequacy. 10% of examinations were re-read by a second blinded examiner (random selection) and intra/interobserver agreement was measured. In no case was ultrasound used as a reference diagnosis, but rather as a predictor.

Histopathology quality assurance

Specimens were immediately fixed in 10% neutral buffered formalin, coded and processed in a standardized manner and evaluated without knowledge of the prediction score. Classification was according to the current two-tier system: hyperplasia without atypia and atypical hyperplasia/EIN. All EIN and carcinoma diagnoses and all diagnostically uncertain cases were reviewed in a blinded fashion and a random 10% of the negative specimens were reviewed. Joint microscopy prior to database lock was used to resolve discordant diagnoses. Concordance statistics and sampling method and specimen adequacy were kept on the audit file.

Integrity of data and safeguards of prediction-models

All ultrasound variables, AUB terminology, PCOS, chronic anovulation, diabetes, and infertility were defined using a prespecified data dictionary that defined hormonal exposure. Data was double entered and range and logic checks were done. Predictor Data were recorded prior to the pathological result. The number of hyperplasia events restricted the degrees of freedom in the models, and non-linearity of the continuous predictors was evaluated. Optimism was estimated using bootstrap internal validation and the final model, intercept, slope and Brier score were kept for external validation. Exploratory cutoffs were not recommended as general biopsy cutoffs.

Results

Of the 354 women evaluated, 21 were excluded for not meeting the criteria for participation, and 13 of the 354 would not participate, leaving 320 women with sufficient specimens for participation. Mean age was 38.1 ± 7.4 years and mean BMI was 28.7 ± 5.2 kg/m². PCOS was documented in 67 women (20.9%), chronic anovulation in 82 (25.6%), and diabetes in 39 (12.2%).

Table 1. Demographic and clinical characteristics (N=320) at baseline.

Characteristic	Value
Age, years	38.1 ± 7.4
Age ≥40 years	143 (44.7)
BMI, kg/m²	28.7 ± 5.2
Obesity (BMI ≥30 kg/m²)	124 (38.8)
Nulliparity	71 (22.2)
History of infertility	63 (19.7)
PCOS	67 (20.9)
Chronic anovulation	82 (25.6)
Diabetes mellitus	39 (12.2)
Hypertension	47 (14.7)
Current hormonal treatment	52 (16.3)
Hemoglobin, g/Dl	10.9 ± 1.8
Anemia	181 (56.6)
Endometrial thickness, mm	10.8 ± 4.2

Data are presented as means ± SD or n (%). BMI – body mass index, PCOS – polycystic ovary syndrome.

The most common main pattern was heavy bleeding, with irregular and mixed bleeding being the next most common patterns. Over 1/3 had symptoms for over 6 months. Women may have similar symptoms but the primary pattern was determined a priori.

Table 2. There are various patterns and characteristics of abnormal uterine bleeding.

Characteristic	n (%)
Heavy menstrual bleeding	102 (31.9)
Irregular menstrual bleeding	69 (21.6)
Intermenstrual bleeding	43 (13.4)
Frequent bleeding	28 (8.8)
Prolonged bleeding	25 (7.8)
Infrequent bleeding followed by excessive bleeding	18 (5.6)
Mixed bleeding pattern	35 (10.9)
AUB duration <3 months	86 (26.9)
AUB duration 3–6 months	111 (34.7)
AUB duration >6 months	123 (38.4)
Bleeding requiring emergency attendance	41 (12.8)
Previous unsuccessful medical treatment	97 (30.3)

AUB – abnormal uterine bleeding. There are no overlaps between categories of principal bleeding pattern.

Sixty-eight women (21.3% of all women) were diagnosed with hyperplasia, 50 without atypia and 18 with atypical hyperplasia/EIN. Seven women (2.2%) had carcinoma and were excluded from the primary model: hyperplasia versus no hyperplasia; 313 women were included in the primary model. Among those 313, the primary outcome frequency was 21.7% (68/313).

Table 3. The histopathological results in women with AUB

Histopathological diagnosis	n (%)
Proliferative endometrium	96 (30.0)
Secretory endometrium	65 (20.3)
Disordered proliferative endometrium	46 (14.4)
Endometrial polyp	38 (11.9)
Hyperplasia without atypia	50 (15.6)
Atypical hyperplasia/EIN	18 (5.6)
Endometrial carcinoma	7 (2.2)
Total	320 (100.0)

EIN – endometrial intraepithelial neoplasia. The diagnosis of carcinoma was reported as a separate entity and not included in the primary binary model.

The women with hyperplasia were older, had a higher BMI, and more commonly had PCOS and chronic anovulation, diabetes, nulliparity, infertility, and AUB that lasted > 6 months. The association between hormonal treatment and hyperplasia, adjusted for the potential confounding factors, was of borderline significance but occurred less often in the hyperplasia group.

Table 4. Clinical or reproductive characteristics of the animals in the different hyperplasia statuses (n=313).

Characteristic	Hyperplasia (n=68)	No hyperplasia (n=245)	p value
Age, years	41.7 ± 5.6	36.9 ± 7.4	<0.001
Age ≥40 years	45 (66.2)	93 (38.0)	<0.001
BMI, kg/m²	32.0 ± 5.1	27.7 ± 4.8	<0.001
Obesity	41 (60.3)	78 (31.8)	<0.001
Nulliparity	23 (33.8)	46 (18.8)	0.009
Infertility	22 (32.4)	39 (15.9)	0.003
PCOS	24 (35.3)	41 (16.7)	0.001
Chronic anovulation	30 (44.1)	48 (19.6)	<0.001
AUB duration >6 months	37 (54.4)	82 (33.5)	0.002
Hormonal treatment	7 (10.3)	43 (17.6)	0.148

Data presented as mean ± SD or as n (%). AUB = abnormal uterine bleeding, BMI = body mass index, PCOS = polycystic ovary syndrome.

There were over two times more women with hyperplasia who had diabetes. The median thickness of the endometrium was 15.0 mm in those with endometrial hyperplasia and 9.2 mm without endometrial hyperplasia. Cystic spaces and heterogeneous endometrium were also found to be significantly associated while the association between focal polyps and leiomyomas were not significant.

Table 5. Metabolic and ultrasonographic features according to the hyperplasia status (n=313)

Characteristic	Hyperplasia (n=68)	No hyperplasia (n=245)	p value
Diabetes mellitus	17 (25.0)	20 (8.2)	<0.001
Hypertension	16 (23.5)	29 (11.8)	0.015
Thyroid disease	8 (11.8)	21 (8.6)	0.423
Endometrial thickness, mm	15.0 (12.3–18.1)	9.2 (7.0–11.8)	<0.001
Endometrial thickness ≥12 mm	55 (80.9)	75 (30.6)	<0.001
Heterogeneous endometrium	38 (55.9)	57 (23.3)	<0.001
Cystic endometrial spaces	25 (36.8)	31 (12.7)	<0.001
Focal endometrial polyp	9 (13.2)	35 (14.3)	0.824
Leiomyoma	14 (20.6)	58 (23.7)	0.590
Polycystic ovarian morphology	22 (32.4)	40 (16.3)	0.003

Data are median (IQR) or n (%). A sonographic thickness was not taken as the reference standard.

All six of the prespecified predictors were kept in the final model. There was an independent association of age, BMI, PCOS, diabetes, chronic anovulation and endometrial thickness with hyperplasia. Univariable analyses suggested that nulliparity, infertility, and duration of AUB were associated and not included in the prespecified model to maintain events per parameter. There were no influential cases that altered inference and variance inflation factors were less than 2.0.

Table 6. The results of the logistic regressions for predicting endometrial hyperplasia (n=313) are listed below.

Predictor	Crude OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Age, per year	1.10 (1.06–1.15)	<0.001	1.08 (1.03–1.13)	0.001
BMI, per kg/m²	1.17 (1.11–1.24)	<0.001	1.10 (1.04–1.17)	0.001
PCOS	2.71 (1.48–4.96)	0.001	2.31 (1.15–4.64)	0.019
Diabetes mellitus	3.75 (1.85–7.61)	<0.001	2.48 (1.14–5.39)	0.022
Chronic anovulation	3.24 (1.82–5.78)	<0.001	2.57 (1.27–5.21)	0.009
Endometrial thickness, per mm	1.40 (1.29–1.51)	<0.001	1.29 (1.18–1.41)	<0.001
Nulliparity	2.21 (1.23–3.97)	0.008	—	—
Infertility	2.53 (1.40–4.56)	0.002	—	—
AUB duration >6 months	2.37 (1.36–4.14)	0.002	—	—

BMI: body mass index, CI: confidence interval, OR: odds ratio, PCOS: polycystic ovary syndrome. Adjusted model was a model that contained the six prespecified predictors.

The best individual continuous predictor was the endometrial thickness with an AUC of 0.816. The apparent AUC value for the combined model was 0.871 (95% CI, 0.823–0.919), the bootstrap-corrected AUC value was 0.858, the Brier score was 0.118, and the calibration slope was 0.93 and the calibration intercept was −0.04. There was no evidence of gross lack of fit as indicated by Hosmer–Lemeshow test (p=0.47). The sensitivity and specificity of the model at the predictive risk threshold of 0.20 were 82.4% and 75.5%, respectively.

Table 7. The diagnostic performance of the individual predictors and the combined model is shown.

Predictor/ model	AUC (95% CI)	Cutoff	Sensitivity %	Specificity %
Age	0.690 (0.621–0.759)	≥40 years	66.2	62.0
BMI	0.731 (0.665–0.797)	≥30.0 kg/m²	60.3	68.2
Endometrial thickness	0.816 (0.760–0.872)	≥12.0 mm	80.9	69.4
Combined clinical model	0.871 (0.823–0.919)	Predicted Risk ≥0.20	82.4	75.5
Combined model, bootstrap corrected	0.858	—	—	—

AUC: area under the receiver operating characteristic curve; BMI: body mass index.

Discussion

In the present study, a clinically significant rate of endometrial hyperplasia was found in the premenopausal women with AUB who were already selected for endometrial sampling. Hyperplasia (histologically confirmed) was present in about one-fifth of the women with 5.6% of them having atypical hyperplasia/EIN; carcinoma was rare but clinically significant. After multivariable adjustment, increasing age, BMI, PCOS, DM, chronic anovulation and increased endometrial thickness were all independent predictors. These results support the idea that risk is a product of the interaction of reproductive, metabolic and sonographic attributes and not the effect of any one of these attributes alone. The simple six predictor model had a good discriminatory performance with a bootstrap corrected AUC of 0.858 and good internal calibration. This was better than age or BMI alone or endometrial thickness alone. Furthermore, the fact that the apparent and the optimism-corrected discrimination are not very different means that there is also some internal stability. These results should however, be viewed as evidence of prediction in the context of the current case mix and not as evidence that the model is ready for clinical implementation. Prediction-model methodology of today needs to be externally validated and evaluated for clinical usefulness before it can be routinely used [30,31]. The frequency of hyperplasia observed should be considered with respect to the population of the study. The women were not a

random sample of the general population of women with AUB but women who had been clinically evaluated and for whom endometrial sampling was indicated. This is important as the incidence of significant pathology is significantly reduced in unselected premenopausal AUB compared to those in whom biopsies have been selected. Pennant *et al.* (2017) showed that the overall absolute risk of endometrial cancer and atypical hyperplasia in the larger population of premenopausal women with AUB was low, and Jha *et al*. (2021) showed that among those with a lower risk of premalignant and malignant disease who had a biopsy, the risk was relatively low [6,16]. This is clinically plausible, and likely to be due to referral and verification enrichment as the higher frequency occurred in the present study. Biopsy is more likely to be performed for women who have persistent symptoms, older age, anovulatory bleeding, metabolic disease, abnormal ultrasound results, and/or failure of conservative treatment. This makes the denominator riskier than all women with AUB and results in higher numbers of risk factors than would be found in all women with AUB. The frequency of 1 in 5 should therefore be called the proportion in clinically selected women sampled and not the prevalence of endometrial hyperplasia in the population of women in Babylon Province. This was also methodologically appropriate as the endometrial carcinoma was separated from the primary hyperplasia outcome. Hyperplasia, especially EIN, is biologically very similar to endometrioid carcinoma, but when these two are mixed, as is done for the heterogeneous composite endpoint, there are not enough data to assess the relative contributions of each component. Some published prediction studies have chosen to use a combined EH/EC outcome, as this outcome is rare, but this may mask any differences between the predictors of premalignant proliferation and predictors of established malignancy [26,27]. In the present approach, a clinically transparent primary endpoint is maintained, but a separate reporting of carcinoma is done. Atypical Hyperplasia/EIN is a lesion that may be associated with an increased risk of subsequent development of invasive epithelial or non-epithelial lesions. Of note is that 5.6% of the women sampled had atypical hyperplasia/EIN identified. EIN is not just a more severe form of benign hyperplasia, but is a pre-cancerous clonal process with much more oncologic significance. Current guidelines and pathological criteria thus distinguish between EIN/atypical hyperplasia and hyperplasia without atypia, as there are material differences in the management and cancer risk [8,9,12]. Systematic reviews have shown a clinically significant risk of concurrent and subsequent endometrial carcinoma in women with an atypical hyperplasia diagnosis, and sometimes, a subsequent diagnosis of endometrial carcinoma is only diagnosed when a more extensive uterine sampling or hysterectomy is performed [13,14]. All of these observations indicate the need for careful histopathological evaluation of atypical lesions and justify the second review of important lesions in the present study, which enhances the diagnostic validity. Meanwhile, there is not complete lack of observer variability when doing histological classification. McCoy et al. (2024) demonstrated that diagnosis of endometrial hyperplasia is still not reproducible, particularly in those lesions that are considered to be diagnostically borderline. Therefore, histopathology is the gold standard, and standardization (and specialist review) are important if there is likely to be a significant difference in management between non-atypical hyperplasia, EIN and well-differentiated carcinoma. All subjects were pre-menopausal, but there was a positive association

with increasing age (hyperplasia) [15]. This agrees with the concept that chronological age during the reproductive years could be an integrative measure of previous hormonal and metabolic exposure. Older premenopausal women have had more opportunity to experience more anovulation, weight gain, insulin resistance, diabetes, infertility or other diseases that are known to be related to prolonged estrogen exposure. The age association should not be used as a definitive cut-off though, for distinguishing between women who definitely need a biopsy and those who do not. More recently, age has been combined with other features such as persistence of bleeding, response to treatment, metabolic risk and ovulatory status to evaluate AUB [2,7]. In the current multivariable model, age remained a predictor even when the other risk factors were included, which further supports this integrated approach: age is an independent predictor and its predictive value is enhanced when considered in combination with other risk factors. It's especially important for younger women. It is possible for a younger woman to have severe obesity, chronic anovulation, diabetes, PCOS and to have persistent AUB and not be identified as a woman with such a condition by relying on the age threshold. On the other hand, if there is no relevant clinical indication, age per se should not be an automatic indication for invasive tests. Thus, the model views age as a risk factor that is added to other risk factors, and not as a single biopsy rule. Among the independent risk factors for the presence of histologically proven hyperplasia, higher BMI was found. This is a biologically plausible and supported by ample evidence of an association between excess adiposity and proliferative endometrial disease. Obese individuals have often been associated with decreased sex-hormone-binding globulin, increased bioavailable estrogen, hyperinsulinemia, inflammatory signaling and altered adipokines and adipocyte tissue promotes peripheral production of estrogen through aromatization. These pathways can be summed up to promote endometrial proliferation together [17,18]. In the present study BMI was modelled continuously, which is important. This is statistically better than a binary BMI (obese/non-obese) classification because classification loses information and suggests an arbitrary cut-off point in the biology of BMI. Further, a continuous association is clinically intuitive – endometrial risk due to adiposity is not likely to start abruptly at a certain BMI. However, one should remember that in the current cross-sectional study, the association is predictive not causal. BMI can also reflect other partially-assessed correlated metabolic factors, such as visceral adiposity, insulin resistance, dyslipidemia, diet and physical activity. Residual confounding can occur even after the adjustments are made. The main clinical implications are that BMI is an easily available parameter that can be added to the stratification of risk for AUB. The present cohort showed that diabetes would be an independent risk factor for about a two-fold increase in the adjusted odds of hyperplasia. There are several biological processes common to diabetes and endometrial proliferative disease such as insulin resistance, hyperinsulinemia, insulin-like growth signaling, chronic inflammatory activity and the common association with obesity. The above mechanisms are also thought to be involved in the association between diabetes and endometrial carcinoma [19]. What is telling is the fact that diabetes remained even after BMI was taken into account. Obesity and diabetes go hand-in-hand, but they are not the same. An additional contribution by glycemic and insulin related metabolic disturbances could be considered if diabetes remains predictive after taking into account body

size. The same trend has been seen in previous prediction studies: diabetes was a main determinant in the premenopausal prediction model created by Giannella *et al.* (2019) and metabolic factors have been important in subsequent prediction studies [26]. Clinically this helps to gain an accurate diabetes history in the assessment of persistent AUB and not just rely on anthropometric appearance. It also proposes that future external validation studies should investigate whether there is any incremental value added to the binary diabetes diagnosis with the inclusion of additional measures like HbA1c or direct measures of insulin resistance. Both of these (PCOS and chronic anovulation) remained as independent predictors. These attributes are very similar but should not be assumed to be the same. PCOS is a multidimensional reproductive-metabolic syndrome which may or may not have hyperandrogenism, obesity, insulin resistance, dysglycemia, infertility and variable ovulatory dysfunction. Chronic anovulation, on the other hand, is directly related to repeated cycles that do not have sufficient progesterone exposure. So, it is biologically plausible that the independent association of chronic anovulation exists. If ovulation does not occur regularly, then the process of secretory transformation and shedding of estrogen stimulated endometrium may not occur for extended periods of time because of the lack of ovulation and, thus, progesterone. If the stimulation persists, then it can lead to hyperplastic change, especially in the presence of obesity/insulin resistance. This mechanism, along with the PCOS overall metabolic and endocrine phenotype, may play a role in PCOS [20]. These findings align with the 2023 International Evidence-Based PCOS Guideline where women with PCOS are known to be at increased risk of endometrial thickening and endometrial cancer; and other risk factors include longstanding, untreated amenorrhea, higher weight, type 2 diabetes, and persistent thickened endometrium [21]. However, the current results and the guidelines do not advocate the routine use of endometrial biopsy in all women with PCOS. Universal invasive testing would place many women at risk for unnecessary testing and the absolute risk is still low enough to warrant this. The better interpretation is prevention that is based on cycle regulation and progestogenic protection as appropriate and prompt evaluation of ongoing or abnormal bleeding based on the full clinical risk profile of the woman. In the current analysis, endometrial thickness was the best single predictor and TVUS has clinical value in the assessment of AUB. Thickening may be a sign of persistent endometrial proliferation and has been shown many times to be linked to important pathology in specific premenopausal and perimenopausal populations. A study by Kumari *et al*., (2022) and another study by Thoprasert *et al*., (2023) showed a strong correlation between rise in ET and endometrial disease with varying suggested thresholds in different populations [22,24]. The exploratory threshold of 12mm used in the present study provided a good balance of sensitivity and specificity for this group of patients, but is not a universal cut-off for diagnosis. The endometrium of the premenopausal uterus is of a different nature than the postmenopausal uterus, and changes significantly throughout the menstrual cycle. Irregular cycles, anovulation, hormone exposure, ultrasonographic technique and presence of intracavitary lesions are also factors that affect measurement [23]. There is strong recent evidence that warns against the use of 12 mm as a cut-off value. The study by Song *et al*. (2025) assessed premenopausal women with AUB and found that even women with ET < 12 mm had some form of premalignant or malignant

pathology [32]. Thus, it is not appropriate to deem a woman without a particular pathology, simply because her endometrium is below a chosen numerical value, if she has significant metabolic or anovulatory risk. This distinction is also supportive and not detractive to the present findings. ET proved to be informative as a continuous predictor, but was superior when used with age, BMI, PCOS, diabetes and anovulation. The bottom line thus is that the thickness of the endometrium has no value, but rather it has value in the context of the clinical picture. Unadjusted analyses showed that the presence of heterogeneous endometrial appearance and cystic spaces were associated with endometrial hyperplasia. The data suggest that sonographic morphology might have clinically important information other than absolute thickness. Since then, the IETA group has created a common vocabulary for the ultrasound characteristics of the endometrium, uniformity, endometrial–myometrial junction, intra-cavitary lesions and vascular patterns, and future studies have shown identifiable ultrasound patterns in different endometrial pathologies [25]. The use of these morphology variables was properly excluded in the main model of this study. First, the number of hyperplasias events will limit the number of parameters that can be estimated without being too optimistic with the model. Secondly, qualitative ultrasound terms are operator-dependent, and may not be as reliable as a standardized thickness measure-ement. Third, the inclusion of other variables should be based on incremental prediction not just on a univariate statistical significance. In future multicenter studies, IETA should be standardized as a set of descriptors and interobserver reproducibility should be assessed, and the added value of morphology after taking the six readily available variables in the present model into account should be evaluated. The main statistical discovery was that the mixed model was significantly superior to the use of age, BMI or endometrial thickness alone. This corroborates the biological and clinical notion of multifactoriality of hyperplasia. A woman with an increased endometrial thickness (moderate risk) and severe metabolic and anovulatory risk might be at different risk of disease than a metabolically healthy woman with a similar sonographic measurement. Discrimination was good with a bootstrap corrected AUC of 0.858, with women with hyperplasia being more likely to have a higher predicted risk than women without hyperplasia. Bootstrap correction is especially useful since the performance in the same data set that the model was developed with tends to be optimistic. Resampling is main to this optimism without sacrificing a significant amount of sample and is important when the number of events is small [30]. But, discrimination is not the only aspect of predictive performance. If a model is to be used to counsel individual patients or to set biopsy thresholds, then the agreement (or "calibration") between the model-predicted and observed probabilities is equally important. The acceptable internal calibration in the present study is encouraging but calibration generally suffers when a model is transferred to another institution or population because the prevalence of the outcome, referral patterns, and predictor distributions, as well as the way the measures are used, varies. This means contemporary reporting guidance now focuses on transparent development, internal validation and then external validation, instead of the AUC on the development sample as a sign of clinical readiness. Therefore, the model should be used as an aid to risk-stratification, and not as a substitute for biopsy, histopathology or well-established AUB recommendations. Ultimately, it could help physicians to determine when

women with a combination of risk factors should be sampled earlier and vice versa, when less aggressive investigation could be considered, if appropriate. This kind of use needs to be proven first in a prospective fashion. The findings from the present study are conceptually similar to previous risk-prediction studies, but for a more specific outcome. Giannella *et al.* (2019) reviewed premenopausal women with AUB and discovered that obesity, diabetes and greater endometrial thickness were significant risk factors for combined endometrial hyperplasia/ cancer. They demonstrated good discrimination in their model, meaning that their model was useful in indicating that it is useful to consider clustering of risk factors and not just individual risk factors [26]. In turn, Srinivas *et al*. (2020) created a risk-scoring system for premalignant and malignant endometrial lesions for women with symptoms who are premenopausal, once more advocating a multi-variate clinical model [27]. Stachowicz et al. (2021) investigated simplified ultrasound-based scoring and Wynants *et al*. (2022) created an IETA-based model that includes ultrasound characteristics in women with AUB [33,34]. Ruan *et al*. (2023) also showed that the clinical and sonographic parameters can be combined in an endometrial malignancy nomogram [28]. The large study by Li *et al*. (2025) is of particular relevance as it specifically focused on premenopausal women, and found overlapping factors – BMI, diabetes, PCOS and endometrial characteristics. But, its end-point was endometrial hyperplasia and endometrial carcinoma. This might be suitable for a wide screening goal, but is not the same as predicting a specific histopathological outcome of hyperplasia [35]. Huang *et al*. (2025) further offered up more recent evidence, creating a model to predict atypical hyperplasia/ endometrial carcinoma in women ages 40-60 years with AUB [29]. The increasing methodological sophistication of prediction research in this field is illustrated by the fact that their model included detailed bleeding characteristics and were externally validated. However, they cover a range of ages from premenopausal to postmenopausal women and the outcome of interest is AEH/EC and not all histologically diagnosed hyperplasia. The present investigation thus is complementary to, but not a repeat of, these investigations. Some of its unique characteristics are focusing on premenopausal AUB, the main outcome being histologically confirmed hyperplasia, the clinical variables being collected prospectively, the clear distinction between hyperplasia and carcinoma, and the clinically simple six variable model, using information readily available in routine practice. These attributes can be useful in a resource-poor environment where complex biomarkers or high-level imaging analysis may not be readily available. The main clinical consequence is that the endometrial sampling should be performed in premenopausal women with AUB based on the sum of the risks and not on any individual risk factor. These factors are age alone, ultrasound thickness threshold alone and PCOS alone are not sufficient reasons to sample universally. Rather, the more risk factors for hyperplasia that are present, the more reproductive, metabolic and sonographic. The present model has the advantage of being easily implemented, because all six predictors are readily available. Age, BMI, PCOS, diabetes, chronic anovulation (history) and TVUS endometrial thickness are readily available without the need for specific tests. This could render the model suitable for use in environments where it would be challenging to use expensive laboratory biomarkers or sophisticated imaging analysis. However, discrimination alone does not provide information about the proper cut point for the

predicted risk to recommend biopsy. Lower threshold values will increase sensitivity but increase the number of biopsies performed and higher thresholds will decrease the number of biopsies, but may result in the loss of clinically important disease. The optimal threshold will thus be influenced by the consequences of a delay in diagnosis of the EIN or cancer, burden of the procedure, local resources, patients' preferences, and background disease prevalence. Decision-curve analysis might be useful to identify if the model has greater net clinical benefit than biopsy-all, biopsy-none or current guideline-based assessment over a range of reasonable risk thresholds [36]. This type of analysis and subsequent prospective impact assessment would be a valuable step towards the use of the model in routine care. Although imaging and prediction techniques have been developed, histopathology is still required for the definitive diagnosis of endometrial hyperplasia and EIN. Risk models are used to estimate risk and are not able to determine glandular architecture or cytological atypia. Likewise, ultrasonography can either increase or decrease suspicion but is not able to differentiate all benign/ hyperplastic, pre-malignant and malignant processes. Quality of sampling also is relevant. Office endometrial biopsy is useful for diffuse endometrial disease, but may underrepresent focal intracavitary disease. Office biopsy and hysteroscopy biopsy samples show that the sampling technique can impact focal abnormality detection [37]. As a result, evidence-based recommendations highlight the need to incorporate clinical risk, ultrasound findings, adequacy of tissue and when indicated, hysteroscopic assessment into a decision to avoid the need to rely on any single investigation alone [7].

Conclusions

Histologically confirmed endometrial hyperplasia was relatively common among the clinically selected premenopausal women with AUB who underwent endometrial biopsy; however, it is important to note that the incidence of endometrial hyperplasia found in this study does not reflect the true prevalence of the condition in this population. Independent predictive information was provided by increasing age, higher BMI, PCOS, diabetes mellitus, chronic anovulation and increasing endometrial thickness. Endometrial thickness was the most significant individual sonographic parameter, but should not be used alone to exclude clinically significant pathology. The good performance of the combined model supports the use of a cumulative-risk strategy based on the interpretation of metabolic, reproductive, and sonographic parameters. The internally validated six-predictor model had good discrimination and calibration and could serve as a practical model for individual risk stratification in a resource-limited clinical setting. At present, however, it should be regarded as an investigational decision support model, and not a substitute for the known indications for biopsy or histopathological diagnosis. Prior to routine implementation, multicenter external validation, recalibration as needed, decision-curve analysis, and prospective evaluation of clinical impact are needed.

Ethics approval and consent to participate: Scientific and ethical approval and hospital permissions were obtained prior to recruitment. Written informed consent was obtained, the sampling was clinically indicated and the study was conducted in accordance with the Declaration of Helsinki.

Data and materials availability: De-identified data can be made available by the corresponding

author upon request and ethics approval and institutional policy.

Conflict of interest: The authors have no competing interests.

Finding

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Authors distribution

All authors had a role in the conception and design of the study, in recruiting and gynecological assessment, in ultrasonography, tissue acquisition, pathology review, data analysis or interpretation, in manuscript revision, final approval and accountability. Individual CRediT roles will be listed on the Journal title page.

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