RESEARCH ARTICLE

A Noninvasive Screening Tool for Abnormal Uterine Bleeding: An Attempt to Reduce Numbers of Endometrial Biopsies

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Abstract

Introduction: Endometrial pathologies contribute to a large proportion of abnormal uterine bleeding (AUB). The aim of this study was to prospectively validate a novel scoring tool [diseases of endometrium–evaluation and risk scoring (DEERS)] as compared with the gold standard histology. Diseases of endometrium–evaluation and risk scoring is a scoring system based on patient characters and endometrial features that are visualized in gray scale transvaginal sonography (TVS). We hypothesized that this tool will help screen women who present with AUB for premalignant and malignant diseases of endometrium, in a noninvasive way. When performed routinely in women prior to subjecting them to endometrial sampling, it would reduce anxiety for the patient till the final histology report is awaited. It may also be used to help reduce the burden of unnecessary samplings to the clinicians as well as decrease the burden of histological slide review for the pathologist.

Materials and methods: A total of 454 women were included. Patients with AUB in whom cervical, myometrial, ovarian, and endocrinal causes were ruled out and were planned for endometrial sampling were recruited for the study, as cases ($n = 284$). Women who were planned for hysterectomy for reason other than endometrial pathologies were taken as controls ($n = 170$). Preoperatively patient characteristics were noted, and TVS was performed to calculate DEERS for all.

Results: In the study cohort, DEERS showed specificity of 100% for cancers, 88.12% for complex hyperplasia, 67.12% for benign lesions, and 76.35% for normal endometrium. However, the sensitivity of prediction was not encouraging. The 95% accuracy of the test for various lesions ranged from 60 to 97%. We noted a high efficacy (sensitivity of 72.2%, specificity of 92.1%) of DEERS in predicting malignant/premalignant diseases of endometrium, when coupled in one group.

Conclusion: This scoring system looks promising for screening endometrial malignancy in women who present with AUB.

Keywords: Endometrium, Screening, Sonography, Uterine bleeding.

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Introduction

Abnormal uterine bleeding (AUB) is one of the common presenting symptoms in gynecological practice. Around 30% of women experience AUB during their lifetime.[1] More than 30% of gynecological visits among premenopausal women and more than 70% of visits among peri and postmenopausal women are because of AUB.[2] The cause of AUB may vary and include polyps, adenomyosis, leiomyoma, malignancy (and hyperplasia), coagulopathy, ovulatory disorders, endometrial, iatrogenic, and not otherwise classified (PALM-COEIN).[3] Endometrial pathologies contribute to a large proportion of AUB during the reproductive years as well as after menopause. AUB that occurs when the uterus is structurally normal, menstrual cycles are regular, and there is no evidence of coagulopathy is likely to have an underlying endometrial cause and is denoted as AUB-E in the PALM-COEIN system. In this system, disorders/lesions of endometrium in actuality are grouped in three different groups (AUB-P, -M, and -E); it is also clinically convenient to arrange endometrial pathologies in a spectrum ranging from disordered proliferation, polyps, hyperplasia, to endometrial malignancy.

Histological diagnosis following curettage or sampling (with or without hysteroscopy) is the gold standard investigation modality to differentiate these endometrial causes of AUB. Presently, there is a lack of clinically available noninvasive tests or biomarkers to differentiate these.[4] Invasive sampling and subjecting it to histological diagnosis is the only confirmatory way to direct treatment and prognosticate the pathologies of endometrium.

Transvaginal sonography (TVS) is a popular primary imaging modality for women with AUB. Although TVS delineates myometrial, ovarian, cervical lesions with efficacy, techniques to differentiate various endometrial causes are not well established. Endometrial thickness (ET) is the only parameter popularly used to

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define endometrial pathologies, which miserably fails to diagnose specific lesions of the endometrium.[5–7]

The aim of this study was to validate a novel scoring tool [diseases of endometrium–evaluation and risk scoring (DEERS)] to determine its efficacy as compared with the gold standard histology. Diseases of endometrium–evaluation and risk scoring is a combination of patient characteristics and TVS indicators to differentiate various endometrial causes of AUB.[8] We hypothesize that this model will help in advance to prognosticate the disease, thus reducing the anxiety for the patient till the final histology report confirms it. It may also help reduce the burden of unnecessary samplings to the clinicians as well as decrease the burden of histological slide review for the pathologist.

Materials and Methods

This prospective case–control study was conducted in a university teaching hospital, in a span of 2 years. Institutional review board approved the study protocol (IEC402/2015).

This study was undertaken to validate encouraging results from a pilot study, in which we developed a scoring system (DEERS) to categorize endometrial pathologies into normal, benign, premalignant, and malignant groups. This scoring system was developed based on our experience and literature review. It includes patient characters and endometrial features that could be visualized in gray scale TVS. The scores were based on multivariate regression analysis from the pilot study conducted on 96 patients who presented with AUB and were found to have spectrum of endometrial pathologies from normal (proliferative/secretory endometrium) to endometrial malignancy. Five experts in the field individually assessed the score for content validity and modifications incorporated as per the suggestions, following detailed discussion (Table 1).

Patients

Patients with AUB in whom cervical, myometrial, ovarian, and endocrinal causes were ruled out and were planned for endometrial curettage were recruited as cases for the study. Patient characteristics were documented. All of these women were subjected to a TVS examination by experts to look for five specific features: ET, endometrial–myometrial (E–M) junction, endometrial echotexture, presence or absence of endometrial polyps, and endometrial collection. The details of TVS evaluation are described below. We also required a group with no endometrial pathology (negative control), for comparison where histological findings of endometrium could be retrieved. Therefore, we chose to take those women who were planned for hysterectomy for reason other than endometrial pathologies. Preoperatively for these controls also, we documented the patient characteristics and performed TVS to calculate DEERS in a similar way (as for the women undergoing curettage).

Sample Size

Anticipating sensitivity of at least 90%, based on our pilot study, with 5% precision and prevalence of endometrial pathology as 5%, at 95% confidence level (CI), a minimum of 81 cases (curettage for AUB) and 162 controls (hysterectomy for indications other than endometrial pathology) were required to be studied.

Scoring System

The scoring system encompasses of two groups—patient characteristics (five) and TVS features (five). Patient characteristics are based on the proven risk factors for endometrial cancer. Individual numeric scores are given to specific characteristics based on the strength of its association with endometrial cancer. Five TVS features were also given a numeric score based on the regression analysis, experts' experience, and available literature (Table 1A). On adding up the numeric values, the minimum possible score is 6 and the maximum is 35 (keeping in mind that a woman can practically be either on hormone replacement therapy (HRT) or tamoxifen, and cannot be on both). Then, we categorized the numeric value obtained into four broad categories: normal endometrium (secretary/proliferative), benign pathologies (polyp, submucus myoma, and simple hyperplasia), premalignant lesions (complex hyperplasia), and endometrial malignancy (Table 1B).

Methodology

After recruitment of women who were planned for curettage or hysterectomy, an informed consent was obtained. Required patient data were elicited and documented. Transvaginal

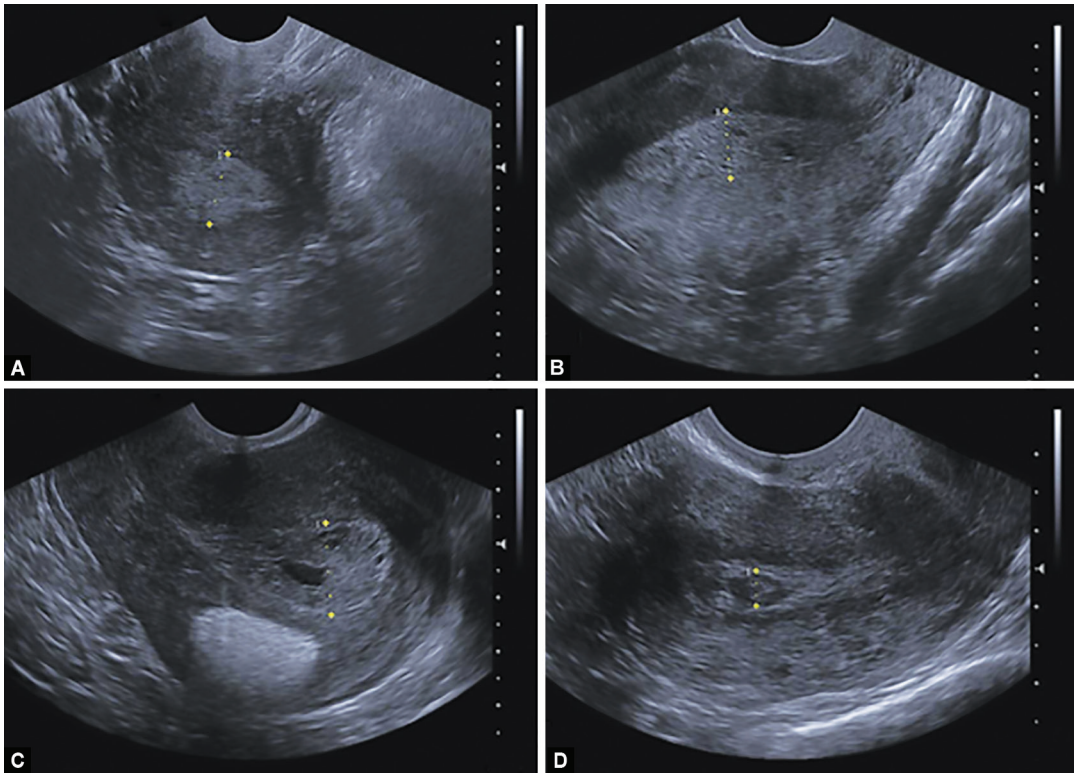
Tables 1A and B: Diseases of endometrium–evaluation and risk scoring system to screen endometrial pathologies by demographic characteristics and transvaginal sonography findings

A: Score allocation system based on demographic and transvaginal sonography findings characteristics—devised after literature review and clinical experience (minimum score: 2 + 4 = 6, maximum score: 13 + 22 = 35)

Demographic characteristic	*Score*
Age	20–40 (score 1), 41–55 (score 2), 56 and above (score 5)
Menopausal status	Premenopause (score 1), post-menopause (score 4)
Diabetes, obesity, hypertension	Score 1 each
HRT	Score 1
Tamoxifen	Score 1
TVS characteristic	*Score*
Endometrial thickness	Up to 5 mm (score 1), 6–10 mm (score 2), 11–20 mm (score 3), >21 mm (score 4)
E–M junction	Distinct (score 1), indistinct (score 5)
Echotexture	Homogeneous (score 1), cystic spaces (score 3), heterogeneous (score 5)
Polyp	Score 4
Endometrial collection	Up to 5 mm (score 1), 6–10 mm (score 2), 11–20 mm (score 3), >21 mm (score 4)

B: Score interpretation for prediction of endometrial pathology (minimum score: 2 + 4 = 6, maximum score: 13 + 22 = 35)

Score	*Interpretation*
6–9	Normal endometrium (secretary/proliferative)
10–15	Benign pathologies: polyp, submucus myoma, disordered proliferation, simple endometrial hyperplasia
16–25	Complex hyperplasia
26–35	Endometrial malignancy



Figs 1A to D: Representative transvaginal sonography pictures from patients depicting prerequisites/principles while obtaining the values for transvaginal sonography features, to ensure reliability and reproducibility: (A) Thick endometrium with indistinct/irregular E–M junction; (B) Thick endometrium with distinct/regular E–M junction with cystic spaces; (C) Thick endometrium with fluid in the endometrial cavity; (D) Thick endometrium with polyp

sonography was performed by an expert using Phillips HD IIXE Ultrasound System (Phillips Ultrasound; Bothell, WE, USA), machine equipped with a multifrequency (6–12 MHz) endovaginal probe. We followed certain prerequisites while obtaining the values for TVS features, in order to ensure reliability and reproducibility. The sagittal section image of uterus (fundus to external os) was focused in a way that it occupied around 75% of the screen and the endometrial lining could be traced from the fundus up to its mergence into endocervical canal down (Fig. 1). In this view, the maximum thickness of endometrium anterio-posteriorly (A-P) was taken (ET). Endometrial–myometrial junction was traced in totality; overall haziness or any breach was scored as indistinct junction. Echotexture was noted as homogeneous, heterogeneous, or with multiple cystic spaces. Polyps, if evident, were recorded as presence or absence. Endometrial collection, if present, was measured A-P at its maximum breadth. A preprocedure/preoperative score was given to every patient, and based on that categorization was done. The pathologist reporting the results of curettage or hysterectomy, however, was blinded to this score. On receiving the final histology report, the diagnosis was allotted a broader category, as the final score (normal, benign, premalignant, and malignant).

Statistical Analysis

The data on categorical variables are shown as percentage. The intergroup comparison of categorical variables is done using Chi-square test or Fisher's exact probability test for a 2×2 contingency table. The diagnostic efficacy measures such as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy along with 95% CI are calculated for DEERS against the outcome of histopathology examination as a gold standard. Multivariate logistic regression analysis is used to obtain the independent determinants of the positivity of disease. The *p* values less than 0.05 are considered to be statistically significant. All the hypotheses were formulated using two-tailed alternatives against each null hypothesis (hypothesis of no difference). The entire data are statistically analyzed using Statistical Package for Social Sciences (SPSS version 20.0, IBM Corporation, USA) for MS Windows.

Results

A total of 470 women fulfilled the inclusion criteria and were enrolled for the study. Seven cases were excluded as the samples were reported inadequate for opinion, whereas in nine cases, endometrium was reported as "pill endometrium" or "lytic endometrium." Therefore, for the final analysis, 454 (curettage/cases: 284, hysterectomy/controls: 170) women were included.

Patient Characteristics

Demographic features of cases and control were statistically similar ($p > 0.05$). Most of the women ($n = 317$, 69.8%) in our cohort belonged to perimenopausal age group (41–55 years). Most women were parous ($n = 403$, 88.8%), and less than a third ($n = 141$, 31.3%) had attained menopause. Around a half (46.5%) were obese [body mass index (BMI) ≥ 25], 16.7% had diabetes, 18.5% had hypertension, and there was considerable overlap as expected among these three comorbidities. The cutoff BMI for overweight and obese were used keeping in mind the different criteria for

Indian Asian population.[8] In our cohort, only one woman was on HRT, whereas four were on tamoxifen therapy.

Out of 284 patients who underwent curettage, the most common indication was postmenopausal bleeding (PMB; *n* = 122, 43%), followed by menorrhagia (*n* = 46, 16.2%), continuous vaginal bleeding (*n* = 42, 14.8%), metrorrhagia (*n* = 40, 14%), amenorrhea followed by excessive bleeding (*n* = 30, 10.6), and tamoxifen with thick ET (*n* = 4, 1.4%). As has been mentioned above, we included 170 women who underwent hysterectomy during the same time span for indications other than endometrial pathology; these acted as controls. Indications of hysterectomy (with or without bilateral salpingo-oophorectomy) were fibroid uterus (*n* = 123, 72%), adnexal masses (*n* = 28, 16.5%), and adenomyosis (*n* = 19, 11.2%).

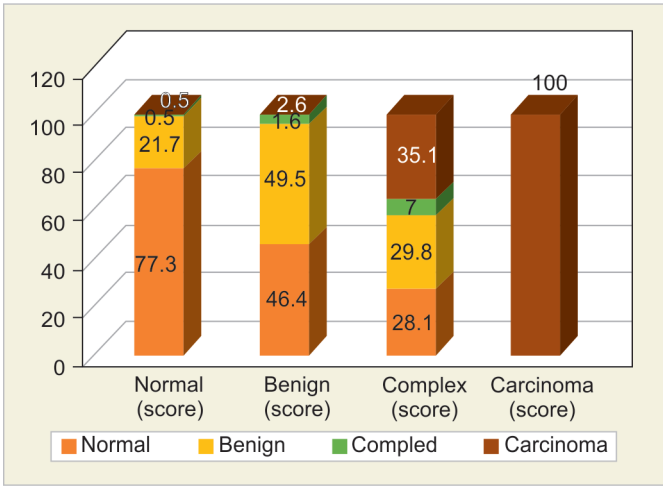


Fig. 2: Comparison of diseases of endometrium–evaluation and risk scoring (calculated prior to curettage/hysterectomy) with the final histopathology report of endometrial tissue

Comparison of DEERS

Comparison of DEERS calculated prior to curettage or hysterectomy with the final histological report of the endometrium showed 100% correlation for endometrial cancer and 77.3% correlation for normal endometrium. While for benign lesions of endometrium, the score could pick up only around half of the cases (49.5%). For complex endometrial hyperplasia, the score could pick up on 7% of the cases (Fig. 2).

Efficacy of DEERS for Individual Categories

On calculating the sensitivity, specificity, PPV, and NPV, we found a wide variation in the efficacy of the test. DEERS showed a good specificity for all the lesions (100% for cancers, 88.12% for complex hyperplasia, 76.35% for normal endometrium, and 67.12% for benign lesions). The 95% accuracy of the test for various lesions ranged from 60% to 97% (Table 2).

Efficacy of DEERS in Predicting Malignancy/ Premalignant Disease

As the major utility of this scoring system is to differentiate lesions that require histology confirmation and surgical intervention, we unified normal and benign categories into one (disease negative), while complex hyperplasia and cancer into one (disease positive). This way, DEERS showed a significant agreement with the overall outcome of histopathology examination (p value < 0.001; Table 3A). We found a sensitivity of 72.2%, specificity of 92.1%, PPV of 44.1%, and NPV of 97.5% for DEERS in prediction of malignancy/ premalignant disease of endometrium (Table 3B).

Table 2: Efficacy (specificity, sensitivity, positive predictive value and negative predictive value) of diseases of endometrium–evaluation and risk scoring for detection of endometrial pathologies as per individual categories

Finding	*Sensitivity*	*Specificity*	*PPV*	*NPV*	*Accuracy*	*95% of accuracy*
Normal	58.57	76.35	75.38	59.85	66.52	62.18—70.86
Benign	59.12	67.12	49.21	75.29	64.32	59.91—68.72
Complex	50.0	88.12	7.02	98.99	87.44	84.40—90.49
Carcinoma	10.71	100.0	100.0	94.75	94.78	92.79—96.77

Tables 3A and B: Efficacy of diseases of endometrium–evaluation and risk scoring in predicting malignancy/premalignant disease: on unifying normal and benign category into one (disease negative) while complex hyperplasia and cancer into one (disease positive)
A: Agreement between DEERS and histopathology

		Histopathology status (gold standard)					
		Positive		*Negative*		*Agreement statistics*	
DEERS		*n*	*%*	*n*	*%*	*Kappa value*	*p value*
Score	Disease positive (*n* = 59)	26	72.2	33	7.9	0.498	0.001*
	Disease negative (*n* = 395)	10	27.8	385	92.1		
	Total (*N* = 454)	36	100.0	418	100.0		

Values are *n* (% of cases). *p* value by Chi-square test. *p* value <0.05 is considered to be statistically significant. *p value < 0.001

B: Efficacy of DEERS for prediction of disease positive cases that require histological confirmation and surgical intervention

	Diagnostic efficacy measures of DEERS with histopathology as a gold standard				
	Sensitivity	*Specificity*	*PPV*	*NPV*	*Accuracy (95% CI)*
Efficacy measures (%)	72.2	92.1	44.1	97.5	90.5 (87.8–93.2)

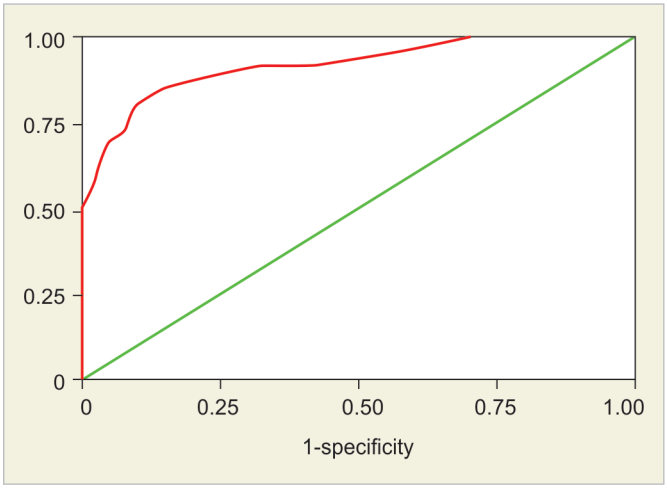


Fig. 3: Receiver-operating characteristic curve to determine test efficacy in predicting premalignant/malignant lesions of endometrium (AUC: 0.916)

Diagnostic Accuracy Measure of DEERS by Receiver Operating Characteristic curve

On plotting receiver-operating characteristic (ROC) curve for disease positive vs disease negative cases, area under curve (AUC) was 0.916, which depicts excellent test results (Fig. 3).

Determination of the Role of Individual Variants for Disease Positivity

On performing multivariate logistic regression analysis for finding the independent determinants of incidence of positivity of disease, menopausal status, obesity, ET, E–M junction, and echotexture, all were found to be independent and significant determinants of incidence of positivity of disease (p value < 0.05; Table 4).

Table 4: Multivariate logistic regression analysis for finding the independent determinants of incidence of positivity of disease

Risk factors (variables included in the model)		*Odds ratio (OR)*	*95% CI for OR*	*p value*
Age group (years)	<40	1.00	—	—
	>40	1.95	0.94–2.97	0.057^{NS}
Parity	Nullipara	1.00	—	—
	Multipara	1.39	0.49–1.76	0.344^{NS}
Menopause	Premenopause	1.00	—	—
	Postmenopause	2.78	1.64–3.83	0.017*
Diabetes	No	1.00	—	—
	Yes	1.88	0.93–2.73	0.095^{NS}
Hypertension	No	1.00	—	—
	Yes	1.83	0.87–2.61	0.106^{NS}
Obesity	No	1.00	—	—
	Yes	2.08	1.11–3.55	0.014*
Tamoxifen	No	1.00	—	—
	Yes	1.51	0.63–2.07	0.388^{NS}
Endometrial thickness (mm)	<10.9	1.00	—	—
	>10.9	3.13	2.09–4.25	0.011*
E–M junction	Distinct	1.00	—	—
	Indistinct	3.23	1.92–5.71	0.006**
Echotexture	Homogeneous/cystic spaces	1.00	—	—
	Heterogeneous	3.98	2.44–6.35	0.001***
Polyp	No	1.00	—	—
	Yes	1.64	0.79–2.14	0.216^{NS}
Endometrial collection (mm)	<6.0 mm	1.00	—	—
	>6.0 mm	1.55	0.65–2.09	0.309^{NS}

OR = 1: reference category. NS, nonsignificant
*p value is statistically significant
**p value is very significant
***p value is highly significant

Discussion

The quest of sonographically visualization of endometrial appearance to device a scoring system with other variables to predict malignancy is not new. Most of these studies have focused on a very specific population of women who present with PMB.[5,10–14]

Endometrial cancer incidence is related to age, with the highest incidence rates being in the age group of 75–79 years. But the age-specific incidence rates rise steeply from age around 45 to 49, necessitating a thorough evaluation of even the premenopausal women who present with AUB.

This is the first study wherein the concept of noninvasive scoring system based on the combination of patient characteristics and TVS features, is used to screen endometrial pathologies among women during their reproductive years as well as after menopause. This study demonstrated high efficacy (sensitivity of 72.2%, specificity of 92.1%) of DEERS in predicting malignant/premalignant diseases of endometrium in women presenting with AUB.

Endometrial pathologies, unlike myometrial, cervical, and ovarian diseases, are difficult to predict with history, examination, and routine imaging procedures. The most popular measure of normal vs abnormal endometrial is ET measured on TVS. However, a cutoff value for normal/abnormal ET still lacks consensus.[6,15–18]

Some other independent methods such as 3D/4D ultrasound, power Doppler, serum markers, and angiography have also been used for screening endometrial cancers.[19–23] Owing to the complexity of test, cost or unavailability of reliable data has limited their use in clinical practice.

As per our knowledge, only one score has been devised to assess the risk of malignancy in the endometrium—risk of endometrial malignancy score.[24] In a cohort of 298 patients, they reported sensitivity and specificity of 93.9 and 95.4% (PPV = 0.91, NPV = 0.95), respectively. However, this scoring system includes human epididymis protein 4 serum marker, which makes it an invasive test.

The histology report in AUB because of endometrial pathology around a third (33%) of times can be due to structurally normal (or variant of normal) endometrium (proliferative/secretary/disordered proliferation) or benign pathologies (polyps, simple hyperplasia) that could effectively be treated with expectant or medical options.[25] We worked on the hypothesis that if we could predict or differentiate these lesions with good efficacy by noninvasive means, it will decrease the burden of curettage and slide reviews. It will also help us prognosticate the disease easily and start treatment immediately, decreasing the patient's anxiety while the patient awaits the results.

In postmenopausal women, too vaginal bleeding is not a rare event, and it represents 10% of gynecological visits.[26] Mostly, this bleeding is because of benign pathologies such as simple

endometrial hyperplasia, endometrial atrophy, or benign polyps. However, PMB should raise high suspicion of being a sign for endometrial cancer or premalignant lesions, which will be the cause in 5–12% of these women.[27]

One of the points which is advantageous for screening of endometrial cancer is its identifiable risk factors. Thus, we tried to exploit this fact in our scoring system. In addition to being of help in screening the women, these risk factors such as diabetes, hypertension, and obesity also pose a higher surgical and anesthesia-related risk.[28,29] Given that only around 10% of PMB is caused by endometrial cancer, the majority of patients undergo surgery unnecessarily with the presence of age-related as well as other surgical risk factors. Hence, a noninvasive way to screen women who must undergo a sampling to confirm the histology and those who do not need it and can be directly started on medical therapy would be a definite advantage for managing these women.

A simple tool that can be used to screen women presenting with AUB primarily to decide the need of an endometrial curettage and further to predict malignancy would be of great benefit in clinical practice. Although a spectrum from normal to malignant endometrium can be detected with this kind of system, the appeal of DEERS lies in its simplicity, cost-effectiveness, noninvasiveness combined with high efficacy in predicting premalignant/malignant lesions of endometrium.

On performing the regression analysis on this bigger cohort, we found that the odds ratio for variables was different when compared with those obtained with the pilot study with a lesser sample size. This analysis can be used to modify the score, validate the results in a fresh cohort, and compare these two scoring systems in terms of their performance with low-risk population.

Conclusion

The quest of sonographically visualization of endometrial appearance to device a scoring system to predict malignancy is not new. All the earlier studies, however, have focused on a very specific population of women who present with PMB. This is the first study wherein a novel concept of noninvasive scoring system to screen endometrial pathologies across ages is used. The results look promising with high efficacy (sensitivity of 72.2%, specificity of 92.1%) to predict endometrial malignancy. The score needs modification to categorize various benign and premalignant lesions.

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