A New Hysteroscopic Risk Scoring System for DiagnosingEndometrial Hyperplasia and Adenocarcinoma

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ABSTRACT

Study Objective: To develop a new hysteroscopic morphologic scoring system that helps physicians, especially those who have less experience, to make a differential diagnosis among normal endometrium (NE), endometrial hyperplasia, and endometrial carcinoma.
Design: A retrospective study (Canadian Task Force Classification II).
Setting: An office hysteroscopy service.
Patients: A total of 435 endometrial biopsies were included in the study: 201 NE, 160 endometrial hyperplasia without atypia(EH), 30 atypical endometrial hyperplasia (AEH), and 44 endometrial cancer (EC).
Interventions: The authors retrospectively evaluated all videos of diagnostic hysteroscopies performed before endometrial biopsies to note endometrial morphologic parameters suggestive of pathology. Principal significant variables were selected by means of the chi-square test ($p<0.05$) and integrated into an ordinal multivariate analysis. Through the estimate of the beta coefficient, a score was obtained to be appointed to each of the selected variables, and characteristic intervals of each of theendometrial lesions were created.
Measurements and Main Results: The scoring system showed a sensitivity and specificity of 71.1% and 80%, 48.7% and 82.5%, 63.3% and 90.4%, and 95.4% and 98.2% regarding NE, EH, AEH, and EC, respectively. The positive predictive valuesand negative predictive values, respectively, were 76.8% and 80% for NE, 62% and 73.5% for EH, 32.7% and 97% for AEH,and 85.7% and 99.5% for EC.
Conclusions: The proposed scoring system showed good diagnostic performance, especially in relation to endometrial cancer, and may represent a useful diagnostic tool, mainly for operators with less experience.

Hysteroscopy, through direct visualization of the uterinecavity, allows for accurate study of the endometrial surfaceas well as a target eye biopsy or the removal of lesions during the same procedure. Different studies have shown that it could be helpful in assessing focal lesions that may bemissed with a dilation and curettage procedure [1,2]. With regard to hysteroscopic diagnostic performance for endometrial lesions, the majority of authors agree that hysteroscopy is associated with good accuracy for the diagnosis of clearly malignant lesions but only moderate accuracy for hyperplasia [3,4].

Some morphologic criteria (Table 1) have been used as hysteroscopic predictors of endometrial hyperplasia (EH) throughout the years. However, these criteria have not been defined based on scientific evidence from controlled randomized clinical trials but rather stem from retrospective trials published between 1987 and 1996 [2,5–7]. Nonetheless, these criteria have been widely used over the past 20 years and are still valid parameters aiding in the differential diagnosis of EH and other benign and malignant conditions/diseases of the endometrium.

There is no agreement in the literature regarding these morphologic and hysteroscopic parameters. To our knowledge, no author has produced a statistical risk model based on hysteroscopic criteria for a differential diagnosis of tumorous endometrial lesions and their precursors. There- fore, the goal of our retrospective study was to create a ''scoring system'' to assist, in particular the less experienced operators, in the differential diagnosis between non pathological endometrium, non-atypical hyperplasia, complex atypical hyperplasia, and well-differentiated endometrioid adenocarcinoma (EC).

Materials and Methods

Selection of Patients

This study involved the retrospective analysis of 522 histologic endometrial biopsies between January 2009 andDecember 2014, with a diagnosis of non-atypical hyperplasia(simple or complex), complex atypical hyperplasia, and ECclassified according to the World Health Organization (WHO) criteria [8]. Three hundred histologic examinationswith a non-pathological endometrial diagnosis (proliferate, secretive, or atrophic), randomly selected through the samecomputerized archive for the same time period, were addedto these data. A total of 822 histologic medical reports of endometrial biopsies were collected, and, subsequently, thenumber of women who had a biopsy performed by a hysteroscopic guide in the setting office was estimated. The computerized archives of the histologic department of our obstetrics and gynecology day clinic unit were consultedto understand how many biopsies were performed and to obtain the videos of the relevant hysteroscopies.

The videos of the relevant hysteroscopies were randomlynumbered, and each one corresponded to the relative histologic examination. Each video was re-evaluated by the same operator who was not aware of the corresponding histologic report, and for each of these, a medical report was compiled.

All videos were re-evaluated from 1 to 3 times consecutively by the same operator who compiled a report (Table 2) containing the identification number of the video examined and the presence or absence of the following morphologic variables: (1) localized endometrial thickening, (2) widespread and irregular endometrial thickening, (3) polypoid endometrial aspect, (4) presence of a singular endometrial polyp, (5) presence of multiple endometrialpolyps, (6) irregular aspect of the polyp, (7) dilated glandularorifices, (8) endometrial cysts, (9) irregular endometrial color, (10) atypical vessels, (11) easy bleeding of endometrialneoplasms, (12) crumbling of the endometrial neoplasms, (13) growth of cerebroid and arborescent aspects, and (14) hematometra. These variables were chosen, considering the parameters reported in the literature, as the main prognostic indicators of hyperplasia or endometrial carcinoma [5,9,10]. Greater details regarding the definitions of each selected parameters are included in Table 2. Patient age at examination, menopausal condition, and the presence or not of abnormal uterine bleeding (AUB) were also extrapolated by our computerized medical records after viewing the videos.

Statistical Analysis

Data obtained by compiling the hysteroscopic reports were then elaborated by comparing them with the relative results from histologic examinations and, thereafter, subdividing them into 4 diagnostic categories: normal endometrium (NE), endometrial hyperplasia without atypia (EH), complex atypical endometrial hyperplasia (AEH), and EC. A descriptive analysis for all hysteroscopic morphologic parameters, menopausal state, the presence of AUB, and patients' age (the only variable in which the analysis of variance test was used Table 3) was performed. Frequency of the morphologic and anamnestic variables examined was evaluated. Any statistically significant difference ($p<0.05$) between the different variables and each of the 4 diagnosticcategories was then calculated with the chi-square test.The principal meaningful variables from a statistical point of view or according to what was indicated in the literature [6,9] were then selected, and these variables were then inserted in an ordinal multivariate analysis. To create the scoring system, we excluded all nonmorphologic parameters, such as menopausal status, AUB and hematometra, non-statistically significant variables ($p>0.05$), ''easy bleeding of the endometrialneoplasm'' because it was too subjective to bereproducible, and parameters with a low chi-

square test. A points system was then constructed using the beta coefficient obtained from multivariate analysis, dividing each of the values by the least prominent and multiplying it by 2 and rounding it off with the closest number [11]. Once the scoring system was obtained, points were calculated for each patient and, maintaining the subdivision in the corresponding diagnostic category, the average, median, andquarters were calculated. Therefore, 4 groups of points were created, considering the intervals between the 25th and 75th percentile of each of the 4 histologic categories (NE, EH, AEH, and EC). Sensitivity, specificity, positive predictive values (PPVs), and negative predictive values (NPVs) of the scoring system for each of these were then calculated.

Results

A total of 822 histologic medical reports of endometrial biopsies were collected. Among the inclusion criteria, besides the presence of biopsies performed by a histologic guide, there had to be the simultaneous acquisition of videorecordings of the hysteroscopies and the patients' case history stored in our day clinic from January 2009 to December2014. Further criteria for selection regarded good quality ofthe video recordings.

Three hundred eighty-seven patients were excluded: 237 for a lack of a hysteroscopic video, 18 because of the poor quality of the images recorded, 79 for a lack of a computerized anamnestic medical report, and 53 because the endometrial biopsies were obtained with a re-examination of the uterine cavity without hysteroscopic procedures.

Of the 435 women included, 201 (46.2%) presented an NE diagnosis (proliferate, secretive, or atrophic); 160 (36.8%) EH, of which 103 were simple and 57 complex;30 (6.9%) AEH; and 44 (10.1%) EC. From the anamnestic chart compiled, together with hysteroscopies, the frequencyof AUB was analyzed, and there was a significant association with hyperplastic lesions and endometrial cancer (χ^2 = 29.5,p <0.0001). Morphologic variables (Table 4) that showed a statistically significant difference included diffuse and irregular endometrial thickening (χ^2 =60.3, p<0.0001), presence of endometrial polyps (singular [χ^2 =23.9,p <0.0001] or multiple [χ^2 = 25.9, p <0.0001]) and irregularaspect (χ^2 =59.1, p<0..0001) (i.e., with heightened areas ofvascularization with superficial ulceration or irregular structures), presence of dilated glandular orifices (χ^2 =15.1,p=0.002), irregular color of the endometrium(χ^2 =117.2, p<0.0001), presence of atypical vessels (χ^2 =262.2, p<0.0001), crumbliness of endometrial neoformations during contact with the tip of the hysteroscope (χ^2 5 227.3, p , .0001) or ease with which they bleed (χ^2 =168, p<0.0001), presence of endometrial neoformations of an arboreous or cerebroid aspect (χ^2 =298.3, p<0.0001), and confirmation of hematometra (χ^2 =26.8, p<0.0001). It is noteworthy that a singular endometrial polyp is the primary presence in nonatypical hyperplasia rather than in atypical and adenocarcinoma cases.

Table 5 shows the 8 variables that at the end of the analysis maintained a statistical significance. From this, in accordance with the literature [11], a practical score was obtainedto allocate to each of the variables. The scoring system started at 0 and reached a maximum value of 40. The pointscalculation for every patient, using the score obtained, allowed us to obtain 4 intervals. The average score and medianof the patients with NE were 1.48 and 0, with a minimum and maximum score, respectively, of 0 and 9 (25th percentile = 0 and 75th percentile = 2); for women with non-atypical hyperplasia, the average, median, minimum, and maximum pointswere 4.93, 4, 0, and 18, respectively (25th percentile = 2 and75th percentile = 7). For non-atypical hyperplasia, the average, median, minimum, and maximum points were, respectively, 12.6, 12, 6, and 22 (25th percentile = 9 and75th percentile = 16), whereas for adenocarcinomas, they were 27.1, 27, 13, and 40, respectively (25th percentile = 24 and 75th percentile = 33).

To choose the lower limits of each interval, the values immediately higher than the 75th percentile of the preceding category were considered, except in the case of NE, in which case we started from 0. Therefore, the lower limits for hyperplasia without atypia diagnosis was 2.01 and for AEH 7.01; for adenocarcinoma diagnosis, a score higher than 16 was necessary. Following this scoring system, although it reduces the specificity of the test comparedwith a diagnostic category, the number of patients with unknown hyperplastic or tumorous lesions was also reduced.

The scoring system showed a sensitivity and a specificity,respectively, of 77.1% and 80% for NE, 48.7% and 82.5% for non-atypical hyperplasia, 63.3% and 90.4% for atypical hyperplasia, and 95.4% and 98.2% for adenocarcinoma.PPVs and NPVs were, respectively, 76.8% and 80% for NE, 62% and 73.5% for hyperplasia without atypia, 32.7% and 97% for AEH, and 85.7% and 99.5% for adenocarcinoma.

Discussion

The value of a hysteroscopic view in the diagnosis of endometrial hyperplasia is still debated in the literature. Gkrozou et al [4] have reported a hysteroscopic sensitivity for carcinoma of the endometrium of 82.6% and a specificity of 99.7%, whereas for endometrial hyperplasia, the sensitivity and specificity are 75.2% and 91.5%, respectively. Ina recent clinical study in which asymptomatic and AUB patients were examined, the authors reported a sensitivity, specificity, PPV, and NPV for endometrial hyperplasia of 81%, 96%, 87% and 93%, respectively, for the AUB group,whereas for asymptomatic women,

the sensitivity was 60%[14]. According to reports from different authors [12,13], narrow band imaging, a new endoscopic technique thatallows for better visualization of the vascular mucosa structure, could improve the diagnostic ability of hysteroscopy for endometrial hyperplasia. Tinelli [12] re- ports a statistically significant difference ($p < 0.005$) regarding the sensitivity of narrow band imaging hysteroscopy to white light (82% vs 56%) in the diagnosis of low-riskhyperplasia. These values of sensitivity and specificity are reduced when the endoscopic examination is performed by less experienced operators [15]. De Marchi et al [15] have reported a respective sensitivity of 60%, 9.09%, and 70% and a specificity of 97%, 98%, and 99.1% with regard to hyperplasia without atypia, atypical hyperplasia, and carcinoma of the endometrium when the hysteroscopy is per- formed by young residents with less than 201 performed hysteroscopies.

Among the morphologic hysteroscopic parameters high-lighted in the literature suggesting endometrial hyperplasia,there is local or diffuse thickening mucous of a papillary and polypoid aspect, with or without an associate glandularcyst; an abnormal vascular network; and a dilated and swollen gland and/or abnormally separated. A growth of the endometrium with a papillary, polypoid, nodular, or mixed aspect showing a consistent brittle area, a necrosisarea, or abnormal vessels is typical of endometrial carcinoma [9,10]. There is still no agreement in the literature with regard to these morphologic and hysteroscopic parameters. Uno et al [5] have pointed out that the only morphologic variable that had an elevated specificity fornon-atypical hyperplasia, showing a striking statistic ofp , .05, was the presence of an endometrial glandular cysticaspect (sensitivity 5 15.8%, specificity 5 97.3%, PPV 5 63.5%, and NPV 5 79.4%), whereas Kurosawa et al [13] have not found hysteroscopic evidence that showsa statistically significant difference for a differential diagnosis between AEH and endometrial carcinoma.

In agreement with what has been reported in the literature [3,4,12,16,17], the sensitivity of hysteroscopy, alsousing our scoring system, is only moderate with regardto AEH, showing a specificity of 90.4% and an NPV of 97%; sensitivity was confirmed at 63.3%. These data are analyzed considering that only 5 patients (i.e., 16.7% ofthe patients with AEH) were classified in a lowercategory than those presented in Table 6, whereas 6 (20%) are inserted in category 4, corresponding to G1 adenocarcinoma. Another issue is the diagnostic performance of our scoring system for non-atypical hyperplasia, which seems to be lower compared with what has been re- ported by some authors [4,15]. In our opinion, this could depend on the presence in the 47 patients with EH, erroneously classified in the ''NE'' group, of only simple hyperplasia without atypia and not a case of complex hyperplasia, contrary to what has been reported in the records of other authors, who, in evaluating the diagnostic accuracy of hysteroscopy, did not divide EH into 2 groups [12], just as, at times, they do not separate hyperplasia without atypia from those with atypia, creating a unique diagnostic category indiscriminately defined as ''endometrial hyperplasia'' [4,6].

Our scoring system showed a higher sensitivity regardingendometrial carcinoma compared with what has been reported by most authors who used a personal evaluation ofthe hysteroscopic view. As far as we understand, this is the only work present in the literature that has selected only EC. Using this scoring system, we were able to correctly classify 42 of the 44 women with an EC histologic diagnosis, reaching a sensitivity, specificity, PPV, and NPV, respectively, of 95.4%, 98.2%, 85.7%, and 99.5%.

The 2 women who were not correctly classified had obtained a score <16, re-entering into group 3, corresponding to AEH (Table 6). Such diagnostic mistakes can be explained by an intrinsic difficulty and, from a microscopic point of view, by differentiating AEH from the EC because the different diagnoses are based mainly on the presence of stroma alteration, which, according to what has been reported by different authors [18,19], has a low reproducibility among different pathologists. In 1999, Bergeron et al [18] proposedsimplifying the WHO classification of 1994 by reducing thediagnostic categories to 3 groups: cyclical endometrium; hyperplasia, which included simple and complex hyperplasiawithout atypia; and ''endometrioid neoplasia,'' which broughttogether AEH and well-differentiated adenocarcinoma. In this study, they reached a medium interobserver percentageagreement of 76% as opposed to the 64% reached by using aclassification with 4 diagnostic categories (cyclical endometrium, endometrial hyperplasia, atypical hyperplasia, and well-differentiated carcinoma) [18]. More recently, Ordiet al [19] have obtained overlapping results with a simplification of endometrial hyperplasia classification, proposing a dichotomization that foresees, on the one hand, non-atypicalhyperplasia and, on the other hand, "endometrioid neoplasia" Considering this, a better sensitivity of hysteroscopy regarding "endometrioid neoplasia" could be achieved by a simplification of the WHO classification system [20]. However, in our opinion, characterizing patients with a precise risk class witha scoring system could be helpful for clinical therapeutic management, especially for patients with AEH, which has arisk of missed diagnosis of endometrial carcinoma that can reach 42.6% [21].

Conclusions

The scoring system that has been proposed has shown good diagnostic performance, in particular regarding G1 endometrioid adenocarcinomas, and could represent an important diagnostic instrument for the diagnosis of AEH and endometrial cancer, especially for less experienced operators. However, given the retrospective nature of our work and the reduced samples representative of AEH, it will be necessary to prospectively validate the results obtained through a

prospective study that also takes interobserver variability into account.

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Table 1 Principal morphologic criteria serving as hysteroscopic predictors of endometrial hyperplasia

- Inhomogeneous polypoid or papillary endometrial thickening, focalor diffuse
- Abnormal vascular patternsPresence of glandular cysts
- Glandular outlets demonstrating abnormal architectural features (thickening, irregular gland density, dilatation)

Table modified with permission from: Nappi C, Di Spiezio Sardo Chapter 5 Endometrial Hyperplasia. A State-of-the-Art Hysteroscopic Approaches to Pa-thologies of the Genital Tract. GmbH (Germany): Endo:Press; 2015:62.

Table 2 Hysteroscpic report used for analysis of each video and definitions of parameters used

Video number:	*(From 1 to 435)*
Variables	**Definitions**
Localised endometrial thickening	Focal thickening of endometrium in a single site of uterine cavity
Widespread and irregular endometrial thichening	Increased and irregular endometrial thickness with multiple mammillated areas
Polypoid endometrial aspect	Homogeneous endometrial thickening with polypoid aspect
Singular endometrial polyp	Single polyp in the uterine cavity
Multiple endometrial polyps	Multiple polyps in the uterine cavity
Irregular aspect of the polyp	Polyp with irregular surface and macroscopic hemorrhagic or necrotic areas
Dilated glandular orifices	Abnormal spacing and dilated glandular opening of yellowish colour
Endometrial cists	Large protruding cist in the uterine cavity
Irregular endometrial colour	Endometrium with grayish-white areas alternated with other hyperemic areas or with hemorrhagic background
Atypical vessels	Presence of vascular distortion, increased capillary density, venulocapillary dilatation alternated with shrinkage of the vessels
Easy bleeding of the endometrial neoplasms	Extremely easy bleeding of endometrial neoplasm at contact with the tip of hysteroscope
Crumbling of the endometrial neoplasm	Easy crumbling of endometrial neoplasm at contact with the tip of hysteroscope
Growth of cerebroid and arborescent aspects	Neoplasm with irregular contour and surface, mammillated aspect, or with polypoid or dendritic projections tentaclelike, which are typically crumbling
Hematometra	Accumulation of blood or menstrual fluid in the uterus

Table 3 Average age of the patients

	NE	EH	AEH	EC	Totale
Total	201	160	30	44	435
Average age (+/- SD)	45,45 (9,7)	50,26 (11,6)	52,73 (12)	60,07 (12,1)	49,2

AEH = complex atypical endometrial hyperplasia; EC = well-differentiated endometrioid adenocarcinoma; EH = endometrial hyperplasia without atypia; NE = normal endometrium; SD = standard deviation.

Table 4 Descriptive analysis and Chi-square test for all the hysteroscopic morphological parameters, a menopausal state, and for the presence of abnormal uterine bleeding.

	Diagnostic categories					
Variables	**NE** *n (%)*	**EH** *n (%)*	**AEH** *n (%)*	**EC** *n (%)*	χ^2	**P**
Localised endometrial thickening	32 (15.9)	24 (15)	7 (23.3)	3 (6.8)	4.030	0.258
Widespread and irregular endometrial thichening	38 (18.9)	51 (31.9)	18 (60)	32 (72.7)	60.234	< 0.0001
Polypoid endometrial aspect	20 (10)	21 (13.1)	4 (13.3)	5 (11.4)	0.990	0.804
Singular endometrial polyp	57 (28.4)	74 (46.3)	9 (30)	5 (11.4)	23.958	< 0.0001
Multiple endometrial polyps	20 (10)	38 (23.8)	12 (40)	14 (31.8)	25.985	< 0.0001
Irregular aspect of the polyp	18 (9)	56 (35)	18 (60)	16 (36.4)	59.026	< 0.0001
Dilated glandular orifices	16 (8)	30 (18.8)	7 (23.3)	2 (4.5)	15.109	0.002
Endometrial cists	6 (3)	22 (13.8)	5 (16.7)	6 (13.6)	16.652	0.001
Irregular endometrial colour	24 (11.9)	59 (36.9)	21 (70)	38 (86.4)	117.276	< 0.0001
Atypical vessels	0 (0)	21 (13.1)	18 (60)	43 (97.7)	262.281	< 0.0001
Easy bleeding of the endometrial neoplasms	2 (1)	9 (5.6)	7 (23.3)	29 (65.9)	168.046	< 0.0001
Crumbling of the endometrial neoplasm	0 (0)	0 (0)	2 (6.7)	26 (59.1)	227.393	< 0.0001
Growth of cerebroid and arborescent aspects	0 (0)	0 (0)	2 (6.7)	33 (75)	298.262	< 0.0001
Hematometra	0 (0)	0 (0)	0 (0)	3 (6.8)	26.844	< 0.0001
Menopause	36 (17.9)	61 (38.1)	17 (56.7)	36 (81.8)	75.547	< 0.0001
Abnormal uterine bleedind	106 (52.7)	84 (52.5)	22 (73.3)	41 (93.2)	29.552	< 0.0001

AEH = complex atypical endometrial hyperplasia; EC = well-differentiated endometrioid adenocarcinoma; EH = endometrial hyperplasia without atypia; NE = normal endometrium.

Table 5 Ordinal multivariate analysis with the main significant variables and their score

Variable	Valuations	b coefficients	p value	95% confidence intervals	Score
Atipical vessels	3.229	7.151	< 0.0001	2.353-4.106	7
Widespread and irregular endometrial thichening	0.988	2.188	< 0.0001	0.499-1.476	2
Dilatated glandular orifices	0.913	2.022	0.004	0.294-1.532	2
Crumbling of the endometrial neoplasm	2.916	6.458	0.007	0.780-5.053	6
Multiple endometrialpolips	0.903	2	0.003	0.314-1.492	2
Irregular aspect of the polyp	1.492	3.304	< 0.0001	0.922-2.061	3
Growth of cerebroid and arborescent aspects	6.341	14.044	< 0.0001	4.254-8.428	14
Irregular endometrial colour	1.678	3.716	< 0.0001	1.159-2.198	4

The 8 variables in the table were the most significant from a statistical point of view or according to what was indicated in the literature [12-13]. The beta coefficient was developed by dividing each of the valuations by the least prominent and multiplying it by 2, and the score was obtained by rounding it off with the closest number.

Table 6 Results obtained for each diagnostic categories using the scoring system

	Diagnosis				
Diagnostic Categories	**NE (%)**	**EH (%)**	**AEH (%)**	**EC (%)**	Total (%)
1	155 (77.1)	47 (29.4)	0 (0)	0 (0)	202 (46.4)
2	43 (21.4)	78 (48.8)	5 (16.7)	0 (0)	126 (29)
3	3 (1.5)	34 (21.3)	19 (63.3)	2 (4.5)	58 (13.3)
4	0 (0)	1 (6)	6 (20)	42 (95.5)	49 (11.3)
Total	201 (100)	160 (100)	30 (100)	44 (100)	435 (100)

AEH = complex atypical endometrial hyperplasia; EC = well-differentiated endometrioid adenocarcinoma; EH = endometrial hyperplasia without atypia; NE = normal endometrium.