

Atrophic endometrium in postmenopausal women referred to diagnostic hysteroscopy: a study to avoid unnecessary examinations

L. GIANNELLA¹, G. DELLI CARPINI¹, J. DI GIUSEPPE¹, D. TSIROGLOU¹, M. PAPICCIO¹, M. MONTANARI¹, A. FREGA², A. CIAVATTINI¹

¹Woman's Health Sciences Department, Gynecologic Section, Polytechnic University of Marche, Ancona, Italy

²Department of Surgery, Medicine and Translational Medicine, Sant'Andrea Hospital, Sapienza University of Rome, Rome, Italy

Abstract. – **OBJECTIVE:** Any diagnostic workup should be based on appropriateness criteria. Diagnostic hysteroscopy is a procedure widely used in endometrial pathology. Its high outpatient feasibility frequently leads to misuse. However, it can cause discomfort and, albeit rarely, complications. The present study aimed to provide an estimate of unnecessary examinations based on variables associated with atrophic endometrium in postmenopausal women referred to diagnostic hysteroscopy.

PATIENTS AND METHODS: One-hundred and sixty-six postmenopausal women undergoing hysteroscopy were retrospectively analyzed. All included women had a final histological reference standard. The sample was divided into women with atrophic endometrium vs. women with endocavitary lesions (benign/premalignant/malignant). Univariate and multivariate analysis was performed to assess those patient characteristics associated with atrophic endometrium. Furthermore, based on the likelihood ratios, a post-test probability analysis was performed to provide an estimate of atrophy according to the presence of specific variables.

RESULTS: Sixty-one postmenopausal women (36.7%) undergoing diagnostic hysteroscopy showed atrophic endometrium at final histology. Multivariate analysis showed that the independent variables associated with atrophy were the absence of abnormal uterine bleeding [Odds Ratio (OR)=6.43, Confidence Intervals (CI) 2.087 to 19.822], and endometrial thickness (criterion < 7 mm) (OR=0.417, CI 0.300 to 0.578). In women showing both variables associated with negative endometrial outcome, post-test probability analysis resulted in an atrophic endometrium rate of 89.13%, from a pre-test probability of 36.7%.

CONCLUSIONS: About 90% of asymptomatic postmenopausal women with endometrial thickness <7 mm resulted in an atrophic endometri-

um at hysteroscopy. Every gynecologist should know and consider these data before referring such women to further examinations. In these cases, diagnostic hysteroscopy is not cost-effective leading to a high number of false positives.

Key Words:

Hysteroscopy, Unnecessary examinations, Atrophic endometrium, Asymptomatic postmenopausal women, Symptomatic postmenopausal women.

Introduction

Endometrial cancer (EC) is the most common gynecological malignant disease in postmenopausal women¹. Unlike ovarian cancer, it is early diagnosed in most cases². Usually, ultrasound evaluation detects endometrial abnormalities. In this regard, the finding of a thickened endometrium in post menopause is often a reason for sending women to diagnostic hysteroscopy. However, based on scientific evidence, women most at risk for malignant endometrial diseases should have abnormal uterine bleeding (AUB)³⁻⁵. In these cases, 10% of women can have EC³. Then, if the ultrasound evaluation measures an endometrial thickness (ET) of less than 4 mm, this rate drops below 1%^{6,7}. In asymptomatic women, the same risk for malignant pathology is reached for a higher ET⁸. Although there are these diagnostic differences in ET between symptomatic and asymptomatic women, management rarely does take this into account. Thus, most postmenopausal women with an ET greater than 4 mm are sent to hysteroscopy, re-

ardless of the presence of AUB. Consequently, this inappropriate diagnostic workup frequently results in a high rate of unnecessary examinations^{9,10}.

It is not so easy to establish whether a useless examination is the one performed without a pre-malignant or malignant lesion on the final histology. Or, if it should only include those hysteroscopies revealing an atrophic endometrium without the presence of intrauterine lesions. Indeed, the presence of benign endometrial lesions, such as polyps, can result in an increased risk of malignant transformation ranging from 2 to 12%¹¹. In these cases, their detection and subsequent removal may make the examination performed appropriately. Furthermore, although it may be a benign lesion, we recognize that explaining to the woman what it is and deciding with her subsequent management can have its importance¹². Consequently, we could define the absence of intrauterine structural lesions with atrophic endometrium at hysteroscopy as an inappropriate procedure.

According to the above data, the present study aimed to provide an estimate of unnecessary examinations based on variables associated with atrophic endometrium in postmenopausal women referred to diagnostic hysteroscopy.

Patients and Methods

This retrospective study included postmenopausal women with AUB and/or thickened endometrium undergoing diagnostic hysteroscopy at the University Hospital of Ancona, Italy, from March 2014 to November 2016. As the present study did not require any further intervention compared to routine procedures, approval from the Ethics Committee was not required. Patients signed written informed consent before each examination.

All included women had to be in menopause with no menstruation from 12 months after 40 years of age. All included women had a histological sampling as the reference standard. In detail, endometrial Vabra (Vacuum aspiration biopsy random assay) in case of negative examination, targeted biopsies in case of suspected neoplastic or preneoplastic lesions, hysteroscopic resection in case of endocavitary structural lesions (e.g., polyps or myomas). Those women with atypical endometrial hyperplasia or cancer underwent a hysterectomy, which represented our histological reference standard.

Diagnostic hysteroscopies were performed in an outpatient setting in vaginoscopy using a 5 mm continuous-flow sheath with a viewing angle of 30°.

Based on the presence of atrophic endometrium at final histology, the sample was divided into women with atrophy *vs.* women with endocavitary uterine lesions (benign/premalignant/malignant). We provided an estimate of unnecessary examinations based on the presence of specific independent variables associated with atrophic endometrium in postmenopausal women referred to diagnostic hysteroscopy.

Our hysteroscopic database was used to collect all data. The following patient characteristics were compared between the two study groups: age (years), age at menarche (years), age at menopause (years), parity, body mass index [BMI = weight (kg)/height² (m²)], presence of hypertension or diabetes, current hormonal replacement therapy (HRT), smoking habit, ET (mm), tamoxifen users, and the presence of AUB.

The Kolmogorov-Smirnov test was used to assess the distribution of continuous variables. Continuous variables were expressed as median and interquartile range. Qualitative variables were expressed as numbers and percentages. Univariate analysis was used to compare the independent variables. The non-parametric Mann-Whitney U-test for two independent samples was used for values that were not normally distributed. The comparisons between categorical variables were performed using the Chi-squared test. Multivariate logistic regression analysis was used to identify variables that associated significantly with atrophic endometrium. All independent variables showing a *p*-value ≤ 0.25 in the univariate model were included in the multivariate analysis¹³. ROC curve analysis was used to calculate the best cut-off value (criterion) for continuous variables associated with atrophy on final histology. After considering our disease prevalence (all cases of atrophic endometrium) as the pre-test probability for unnecessary examinations, the likelihood ratio was used to calculate the post-test odds from the pre-test odds of disease: post-test odds = pre-test odds x likelihood ratio. The relation between odds and probability is as follows: odds = $P/(1-P)$ and $P = \text{odds}/(1+\text{odds})$. Using these equations, we could calculate the post-test probability of disease from the pre-test probability of disease^{14,15}.

Table I. Final histology of all included postmenopausal women undergoing diagnostic hysteroscopy.

Final histology					
Atrophy	Cancer	Hyperplasia	Myoma	Polyp	Total
61 (36.7%)	15 (9.0%)	11 (6.6%)	14 (8.4%)	65 (39.2%)	166 (100.0%)

All statistical analyses were performed using MedCalc Statistical Software Version 19.0.3 (MedCalc Software BVBA, Ostend, Belgium; <https://www.medcalc.org>; 2019). $p < 0.05$ was considered to indicate statistical significance.

Results

One-hundred and sixty-six consecutive postmenopausal women undergoing diagnostic hysteroscopy were included in this study.

Histological examination revealed the presence of 61 (36.7%) women with atrophic endometrium, 15 (9.0%) women with EC, 11 (6.6%) women with endometrial hyperplasia (4 atypical and seven non-atypical), 14 (8.4%) women with submucosal myoma, and 65 (39.2%) women with endometrial polyps (Table I).

Patient characteristics showed no significant differences between women with or without

atrophic endometrium at final histology about age, age at menopause, diabetes, hypertension, HRT users, smoking habit, tamoxifen users (Table II). Conversely, significant differences were present concerning age at menarche ($p=0.006$), AUB ($p<0.001$), BMI ($p=0.025$), and endometrial thickness ($p<0.001$) (Table II).

Multivariate analysis showed that an endometrial thickness of less than 7 mm associated with atrophic endometrium on final histology [odds ratio (OR)=0.417, 95% confidence intervals (CI) 0.30-0.57]. Likewise, the absence of AUB correlated with atrophic endometrium (OR=6.43, 95% CI 2.08-19.82) (Table III).

Post-test probability analysis showed that the simultaneous presence of both independent variables led to a rate of atrophic endometrium of 89.13%, from a pre-test probability of 36.75 (Table IV).

The best cut-off level for the highest sensitivity and specificity for ET value was < 7 mm (sensitivity 0.852, specificity 0.876) (Figure 1).

Table II. Univariate analysis comparing women with or without atrophic endometrium.

Independent variables	Women with atrophic endometrium (61) n (%)	Women with endocavitary lesions (105) n (%)	p-value
Age (median and interquartile ranges)	60 (56.0-69.0)	61 (56.75-70.0)	0.406
Age at menarche (median and interquartile ranges)	13 (12.0-14.0)	12 (11.0-13.0)	0.006
Age at menopause (median and interquartile ranges)	52 (48.75-54.0)	51 (50.0-53.0)	0.685
Abnormal uterine bleeding	16 (26.2)	80 (76.2)	< 0.001
Body Mass Index			0.045
< 18.5	1 (1.6)	3 (2.9)	
18.5-24.9	20 (32.8)	15 (14.3)	
25-29.9	23 (37.7)	49 (46.7)	
≥ 30	17 (27.9)	38 (36.2)	
Diabetes	6 (9.8)	13 (12.4)	0.620
Hypertension	24 (39.3)	52 (49.5)	0.205
Nulligravid	3 (4.9)	18 (17.1)	0.022
HRT users	14 (23.0)	30 (28.6)	0.430
Smoking habit	12 (19.7)	12 (11.4)	0.146
Tamoxifen users	3 (4.9)	6 (5.8)	0.816
Endometrial thickness (mm) (median and interquartile ranges)	5 (4.0-6.0)	9 (7.0-12.0)	< 0.001

HRT: hormonal replacement therapy.

Table III. Logistic regression analysis showing variables associated with atrophic endometrium.

Independent variables	Odds ratio	95% CI	p-value
Age at menarche	1.297	0.909 to 1.850	0.151
Endometrial thickness	0.417	0.300 to 0.578	< 0.0001
Abnormal uterine bleeding = no	6.432	2.087 to 19.822	0.0012
BMI (18.5-24.9)	1.421	0.345 to 5.846	0.625
BMI (≥ 30)	1.469	0.395 to 5.460	0.565
BMI (< 18.5)	0.167	0.004 to 6.532	0.338
Nulligravid	0.205	0.030 to 1.392	0.105
Hypertension = yes	0.4282	0.126 to 1.453	0.173
Smoking habit = yes	2.329	0.486 to 11.154	0.290

BMI: body mass index; CI: confidence intervals.

Discussion

The present study showed that about 90% of asymptomatic postmenopausal women with ET <7 mm had an atrophic endometrium at final histology.

We are well aware that in clinical practice, women with and without AUB are managed in the same way, although only symptomatic women with endometrium > 3 mm are really at risk of EC¹⁶. In a previous study, 93.2% of diagnostic hysteroscopies performed in asymptomatic postmenopausal women with ET greater than 5 mm were defined as useless¹⁷. This is because none of them encountered an endometrial malignant or pre-malignant lesion. However, other authors reported a

cancer rate on asymptomatic polyps ranging from 2.6% to 3.9%^{18,19}. The absence of endocavitary structural lesions with atrophic endometrium is likely to represent the occurrence with the lowest risk for severe endometrial lesions. Therefore, we decided to divide our sample between women with and without atrophic endometrium. We have lowered the cut-off value to define a diagnostic hysteroscopy as an inappropriate procedure in order not to affect the negative predictive value.

Any diagnostic workup should be based on appropriateness criteria. Diagnostic hysteroscopy is a procedure widely used in endometrial pathology, as well as sonohysterography²⁰⁻²². Its high outpatient feasibility frequently leads to misuse. However, it can cause discomfort and, albeit rarely, complications²³. In this field, asymptomatic postmenopausal women with a “thickened” endometrium represent a challenging clinical situation.

In a fascinating study, Scrimin et al²⁴ defined inappropriate hysteroscopies the following cases: (1) asymptomatic postmenopausal women without polyp at ultrasound; (2) asymptomatic postmenopausal women with polyp at ultrasound having a mean diameter < 18 mm; (3) symptomatic women with ET < 4 mm and sharp demarcation. The authors reported that in their clinical practice, they often evaluated asymptomatic postmenopausal women with a thickened endometrium: in 58% of cases, they only revealed endocavitary synechiae. Smith-Bindtman et al⁸ showed that an ET of 11 mm places asymptomatic women at the same risk of EC as symptomatic women with an ET of 5 mm. Ozelci et al²⁵ suggested an endometrial thickness of 10.5 mm as a cut-off to further examinations in asymptomatic postmenopausal women. Other studies^{26,27} found a cut-off value > 8 mm as the best ET to detect

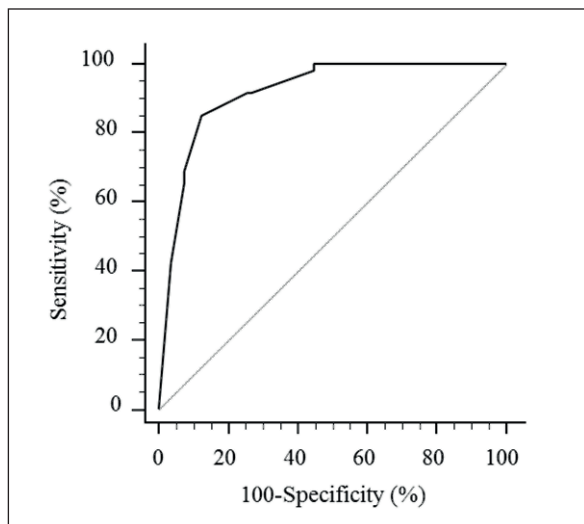


Figure 1. ROC curve for endometrial thickness values associated with atrophic endometrium. The AUC was 0.917 (95% CI 0.875 to 0.958, $p < 0.001$). The cut off level for the greatest sensitivity and specificity was < 7 mm (sensitivity 0.852, specificity 0.876).

Table IV. Pre- and post-test probability for endometrial atrophy at final histology according to the presence of specific independent variables.

Independent variables	Pre-test probability (%)	Likelihood ratio	95% CI	Post-test probability (%)
Absence of AUB or ET < 7 mm	36.75	0.922	0.536 to 1.586	34.88
Absence of AUB and ET < 7 mm	36.75	14.115	5.895 to 33.798	89.13

AUB: abnormal uterine bleeding; ET: endometrial thickness; CI: confidence intervals.

endocavitary structural lesions in asymptomatic postmenopausal women. However, the predictive value of ET changes a lot between symptomatic and asymptomatic women. It was less accurate in women without AUB²⁸.

In this regard, the present study showed that only the simultaneous presence of both independent variables (absence of AUB and endometrial thickness <7 mm) associated with negative endometrial outcomes. The presence of a single variable (absence of AUB or endometrial thickness < 7 mm) did not increase the post-test probability for atrophic endometrium (Table IV). In our asymptomatic postmenopausal women with ET < 7 mm, there was no case of EC or atypical endometrial hyperplasia. There were five women out of 46 (10.9%) with benign endometrial polyps. So, gynecologists should know that in such clinical situations, only one woman out of ten will have a benign endocavitary structural lesion. In these cases, diagnostic hysteroscopy is not cost-effective leading to a high number of false positives. Based on this risk-benefit ratio, conservative management may be an option. However, the decision-making process could take into account the presence of other recognized risk factors, such as obesity or diabetes, even if no associations were found in our study.

The present study has the limitation of being retrospective. Some independent variables of importance may be missing. Although all examinations were performed in a single Clinical Centre, both diagnostic and operative procedures could not be standardized. A strength of the study is represented by the fact that each woman had a histological examination as a reference standard.

Conclusions

Limited to the study population, about 90% of asymptomatic postmenopausal women with ET <7 mm resulted in an atrophic endometrium

at hysteroscopy. In this population, there was no case of EC or atypical endometrial hyperplasia. Every gynecologist should know and consider these data before referring such women to diagnostic hysteroscopy.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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