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Office Endometrial Cytological Sampling: Examining Predictors of Strenuousness

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Abstract. *Background/Aim: Endometrial cytology is an alternative perspective for the diagnosis of endometrial cancer. The present study examined the potential risk factors for strenuousness in endometrial cytology sampling. Patients and Methods: One hundred and eighty-one women who underwent endometrial cytological sampling with the Endogyn curette participated in the study. Strenuousness in obtaining the sample was graded into a five-level scale-score. Various parameters were assessed in association with the strenuousness score. Multivariate ordinal logistic regression analysis was performed. Results: Postmenopausal status (adjusted OR=2.63, 95%CI=1.52-4.56, p=0.001) and previous invasive/surgical procedures in the cervix (adjusted OR=2.15, 95%CI=1.10-4.24, p=0.026) were associated with higher strenuousness score. Participants' age at sampling, phase of menstrual cycle, endometrial thickness, obesity, current hormonal use and reproductive history of women were not significantly associated with the strenuousness of the procedure. Conclusion: Increased difficulty during endometrial sampling is noted in postmenopausal women, and in patients with previous surgical procedures in the cervix.*

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The incidence of endometrial cancer (EC) is increasing and currently it is estimated that EC is the fifth most common cancer in women worldwide, with approximately 150,000 new cases diagnosed each year (1). Common risk factors for EC include use of hormonal replacement therapy tamoxifen treatment, subfertility *per se*, hereditary genetic factors, obesity and diabetes mellitus (2-8).

Diagnosis of EC is based on medical history, clinical examination and imaging tests, while definite confirmation of diagnosis is solely achieved by tissue sampling and histopathological examination. Medical history of the patient is crucial, with regards to the existence of risk factors. Transvaginal ultrasound appears to be a preferable approach, compared to abdominal, in terms of accuracy (9, 10). Computed Tomography and Magnetic Resonance Imaging are useful tools, and used for the clinical staging of EC, whereas Positron Emission Tomography can add to the sensitivity of both techniques in certain cases (11-13). The gold-standard method for the diagnosis of EC remains hysteroscopy with targeted biopsy and curettage. In cases where clinical symptoms persist, repetition of sampling is mandatory, even in the presence of a negative histopathological report (14).

Cervical cytology is an easy and relatively inexpensive screening method with well-established effectiveness (15). Endometrial cytology represents an alternative perspective for the diagnosis and potential screening for EC (16). Several devices have been scheduled for the sampling of the cytology specimen, such as Endocell (17), Endogyn (18), Endosampler (19), Endoscan (20), Novak curette (21), Pipelle (22, 23), SAP-1 (24) Tao brush (25-27) and Vabrasio (28) (Table I). Conventional cytology is not widely applied for the diagnosis

Table I. *Devices currently used for the sampling of the endometrium.*

Device	Key information about the technique in the clinical setting
Endocell	Comparable to manual vacuum aspiration, but with significantly less pain (17).
Endogyn	Complementary to dilatation and curettage for the diagnosis of endometrial lesions; it can be performed before dilatation and curettage and/or hysterectomy (18).
Endosampler	Utilized for sampling of endometrial tissue. The design of this device may allow for superior accuracy and a more reliable sample than traditional endometrial sample devices (19).
Endoscan	The instrument may be used for the screening of high-risk groups for endometrial cancer, and to investigate postmenopausal bleeding. Cell blocks suitable for staging of the endometrial cycle can be obtained from women with infertility (20).
Novak curette	The oldest device; often used as the reference-comparison method for other devices (21).
Pipelle	Pipelle biopsy appears to be as effective as the Novak curette in obtaining an adequate specimen for histologic analysis and is associated with less pain (22,23).
SAP-1	Endometrial cytology using SAP-1 sampling device and SurePath preparation may be a reliable approach for screening patients with endometrial carcinoma and its precursors (24).
Tao brush	A reliable uterine sampling device that performs well as a diagnostic tool for outpatient assessment of the endometrium of women with patent cervices. Women with tight or stenotic cervices are poor candidates for endometrial brushing, and may experience pain if the procedure is attempted (25, 26). High sensitivity and specificity for the detection of endometrial hyperplasia and endometrial carcinoma have been documented (27).
Vabrasio	Device with good diagnostic reliability regarding endometrial cancer, but has some shortcomings due to insufficient sampling for diagnosis (28)

of histological endometrial abnormalities; in contrast, liquid-based cytology is a more effective method for the endometrial specimen processing, offering valuable information on the phase of menstrual cycle and the existence of hyperplasia with or without atypia or malignancy (29).

Strenuousness can arise during the retrieval of an endometrial cytological sample. Importantly, in certain cases, the strenuousness may be severe to the degree that proper sampling is not possible and thus the cytological specimen is inadequate, often leading to a false diagnosis. The current study aims to evaluate the association of potential risk factors with strenuousness in endometrial cytology sampling. To our knowledge, no such data have been previously reported and risk factors associated with the procedure of endometrial sampling have not been identified at this level.

Patients and Methods

Patient selection. One hundred and eighty-one patients, admitted to the Outpatient Gynecological Oncology Unit of the 3rd Department of Obstetrics and Gynaecology, in "Attikon" University Hospital, Athens, Greece, from September 2009 to October 2015, were included in the study. A detailed medical history was recorded, along with an endometrial cytological sampling retrieved from all participants. Written informed consent was obtained for all participants before their enrollment in the study, following a detailed acknowledgement on the purpose and details of the study. The study is in agreement with the Helsinki Declaration and has been approved by the local Institutional Review Board of the "Attikon" Hospital (4/30-04-2009, issue number 15).

For the sampling procedure, the Endogyn curette was used (BIOGYN S.N.C., Mirandola, Italy). The procedure was completed in an outpatient "office" setting and patients received neither local nor general analgesia or anesthesia. The endometrial sample was directly embedded in a Cytolyt solution (Cytyc Corporation, Marlborough, MA, USA) that has hemolytic, mucolytic and proteolytic properties. The whole procedure took place according to the manufacturer's instructions. Two independent expert cytopathologists (PK and NM) examined the samples and provided the cytological diagnoses.

Factors recorded and evaluated for the study include: age of the participant, obesity [body mass index (BMI) ≥30 kg/m^2], reproductive history and characteristics (menopausal status, phase of the menstrual cycle, number of previous pregnancies/vaginal deliveries/vacuum-assisted deliveries/cesarean sections) history of invasive/surgical procedures in the cervix and current use of hormones), clinical indication for cytological examination and endometrial thickness, as assessed by transvaginal ultrasonography (30) at the day of the sampling. Data were recorded in an Excel file and cross-checked with the participants hospital records.

The strenuousness of the procedure was calculated through a five-level scale (scores 0-4). Level 0 was defined as total lack of strenuousness in obtaining the sample; level 1 (light strenuousness): as need to alter the uterine position-axis to facilitate access to the cavity; level 2 (moderate strenuousness): as need to use a tool to insert the endometrial swab in the cavity, but without any need to hold the cervix; level 3 (high degree of strenuousness): as need to use a mize forceps to hold the cervix and/or the use of a metal probe to enter the cervix; level 4 denotes the unfeasibility in obtaining a sample.

Statistical analysis. The factors associated with the strenuousness score were evaluated using a two-step approach: namely, a univariate and a multivariate analysis. At the univariate analysis, non-parametric tests, namely Mann-Whitney-Wilcoxon (MWW) test for independent samples or Spearman's rank correlation coefficient, were implemented given the deviation from normality of the score

Table II. *Description of demographic, reproductive history and clinical characteristics of the study sample (n=181).*

Categorical Variables	N (%)
Clinical indication for cytological examination	
Abnormal vaginal bleeding	39 (21.5)
Abnormal imaging finding	47 (26.0)
Abnormal Pap test result	3 (1.7)
Presence of endometrial cancer risk factors	92 (50.8)
Menopausal status	
Pre-/perimenopausal	110 (60.8)
Postmenopausal	71 (39.2)
Cycle phase (among pre-/peri-menopausal women)	
Proliferative/ovulation	64 (58.2)
Secretory	46 (41.8)
Overweight/obesity	84 (46.4)
Previous invasive/surgical procedures in cervix	32 (17.7)
Current hormone use	19 (10.5)
Previous cesarean sections	24 (13.3)
Previous vacuum-assisted deliveries	7 (3.9)
Numeric Variables	**Mean±SD (range)**
Age at diagnosis (years)	50.3±13.0 (25-90)
Endometrial thickness (mm)	6.4±3.6 (1.5-24)
Previous pregnancies	2.5±1.6 (0-10)
Previous deliveries	1.7±1.1 (0-8)

Categorical variables are presented as frequency (percentage), whereas numeric variables as mean±SD (range).

(as attested by the Shapiro-Wilk test). The statistical analysis performed in each case is denoted within the text.

At the multivariate analysis, ordinal logistic regression was performed with the strenuousness score set at the dependent variable. The factors found to be significantly associated with the strenuousness score at the univariate analysis were further examined as independent variables. Following the final model, after mutual adjustment, only statistically significant variables were included (backward selection statistical procedure). The satisfaction of the proportionality-of-odds assumption was evaluated with the appropriate likelihood ratio test. Statistical analysis was performed with STATA version 13 statistical software (Stata Corporation, College Station, TX, USA).

Results

Patients' clinical characteristics are presented in Table II. Mean age of participants was 50.3±13.0 years. The most common clinical indication for the cytological examination was the presence of EC risk factors (50.8%). Sixty-one percent of the participants were pre/peri-menopausal; among them, 58.2% specimens displayed endometrial proliferative phase or ovulation. Previous invasive/surgical procedures in the cervix were reported in 32 participants (17.7%); 12 participants had undergone cervical conization; 14 participants had previous cervical sutures after ripening during vaginal delivery; three patients had undergone removal of cervical polyps; and another three have had cervical cerclage. The number of pregnancies in the recruited population ranged between 0 and 10 (mean=2.5±1.6); thirty-three women (18.2% of the total sample) had never been pregnant before; the number of deliveries ranged between 0 and 8 (mean=1.7±1.1). Cytological sampling was adequate in 83.4% (166/181) of cases, on the assessment of the experienced performing gynecologist.

Table III. *Diagnoses yielded by the endometrial cytology.*

Diagnosis	N (%)
Normal endometrium	92 (50.8)
ACE-L	43 (23.7)
ACE-H	3 (1.7)
ACE-US	3 (1.7)
Endometrial cancer	3 (1.7)
Failure/inadequate sample	37 (20.4)

ACE: Atypical Cells of Endometrium with low (ACE-L) or high (ACE-H) probability for malignancy; ACE-US Atypical Cells of Endometrium of undetermined significance.

The final diagnoses yielded by the endometrial cytology are presented in Table III. Cytological analysis identified normal endometrium in 50.8% of cases; Atypical Cells of Endometrium with Low probability for malignancy (ACE-L) in 23.7%; High probability for malignancy (ACE-H) in 1.7%; Uncertain probability for malignancy (ACE-US) in 1.7%; and EC in 1.7%. Failure in the procedure or inadequate sample was recorded in 20.4% of the total sample.

Statistical analysis (Table IV) showed that participants' age positively correlated with the strenuousness score during the procedure (Spearman's rho=+0.246, p=0.0008); accordingly, postmenopausal women were associated with higher strenuousness score (2.01±1.37 *vs*. 1.31±1.21 for pre-/peri-menopausal, p=0.0005, MWW). Women who had undergone previously invasive/surgical procedures in the cervix also presented with higher strenuousness score (2.06±1.29 *vs*. 1.48±1.29 for women free of interventions, p=0.020, MWW).

On the other hand, no differences were observed regarding obesity (p=0.109, MWW), the phase of the menstrual cycle (p=0.307, MWW), current hormone use (p=0.192, MWW), number of previous pregnancies (Spearman's rho=0.101, p=0.175), number of previous deliveries (Spearman's rho= +0.077, p=0.301), previous vacuum-assisted deliveries (p=0.482, MWW), previous cesarean sections (p=0.693, MWW) and endometrial thickness (Spearman's rho=–0.084, p=0.262) (Table IV).

Table IV. *Results of the univariate analysis.*

Variables	Difficulty score (mean±SD)	*p*-Value
Age at diagnosis (years)§		0.008[S]
<Median (48 years)	1.31±1.21	
≥Median (48 years)	1.84±1.35	
Weight status		0.109[MWW]
Normal weight/underweight	1.43±1.26	
Overweight/obese	1.76±1.35	
Menopausal status		0.0005[MWW]
Pre-/perimenopausal	1.31±1.22	
Postmenopausal	2.01±1.37	
Cycle phase (among pre-/peri-menopausal women)		0.307[MWW]
Proliferative/ovulation	1.39±1.19	
Secretory	1.20±1.26	
Previous invasive/surgical procedures in cervix		0.020[MWW]
Yes	2.06±1.29	
No	1.48±1.29	
Current hormone use		
Yes	1.95±1.31	0.192[MWW]
No	1.54±1.31	
Previous pregnancies§		0.175[S]
Never	1.32±1.17	
Ever	1.64±1.33	
Previous deliveries§		0.301[S]
Nulliparous	1.36±1.14	
Parous	1.64±1.34	
Previous vacuum-assisted deliveries		0.482[MWW]
Yes	1.29±1.49	
No	1.60±1.30	
Previous cesarean sections		
Yes	1.71±1.37	0.693[MWW]
No	1.57±1.30	
Endometrial thickness (mm)§		0.262[S]
<Median (6 mm)	1.71±1.40	
≥Median (6 mm)	1.47±1.21	

Difficulty score (mean±SD) in the various sub-groups. Bold cells denote statistically significant differences. §Variables are presented in categories for purely descriptive purposes; they were treated as numeric variables in the analysis and therefore the Spearman's rank correlation coefficient was implemented; MWW: Mann-Whitney-Wilcoxon test for independent samples; S: Spearman's rank correlation coefficient.

The results of the multivariate ordinal logistic regression analysis examining factors independently associated with the strenuousness score, are presented in Table V. Patients' age lost its statistical significance during the multivariate backward selection of variables, but the effect of menopausal status and previous invasive/surgical procedures in the cervix were robust enough to persist. Specifically, postmenopausal status (adjusted OR=2.63, 95%CI=1.52-4.56, postmenopausal *vs.* pre-/peri-menopausal, p=0.001) and previous invasive/surgical procedures in the cervix (adjusted OR=2.15, 95%CI=1.10-4.24, yes *vs.* no, p=0.026) were found to be independently associated with a higher strenuousness score.

Discussion

The present study is the first to validate predictors for strenuousness in endometrial cytological sampling in the general population. We applied the technique in an office setting, without the need of prior preparation of the cervix, drug administration (31, 32), special equipment or devices. Postmenopausal status and previous invasive/surgical procedures in the cervix emerged as two independent factors, leading to a more than two-fold increase in the risk of undergoing a strenuous sampling procedure. Increased age appeared to merely reflect the aforementioned association between postmenopausal status and increased strenuousness of the procedure.

Previous cervical interventions could evidently impair the access to the uterine cavity, due to the frequent adhesions they induce in the endocervix. Also, menopausal status, cervical atrophy and cervical "shrinking" in postmenopausal women (33), may prohibit the effective sampling of endocervical canal and the uterus. Besides, uterine prolapse is more frequent in postmenopausal women (34) and this usually changes the uterine position, rendering the endometrial cytology sampling procedure more challenging.

In our study, obesity, phase of the menstrual cycle, current hormonal use, number of previous pregnancies, deliveries, vacuum-assisted deliveries, and cesarean sections, as well as endometrial thickness were not significantly associated with strenuousness in obtaining an adequate sample. It, therefore, seems interesting to contrast between the vaginal delivery-associated effects, which appeared rather mild, and the more severe effects of invasive procedures in the cervix, which were more likely to raise the strenuousness of the procedure. The fact that the aforementioned list of factors did not lead to increased strenuousness of the procedure, might be linked to the sampling method *per se*, indicating its ability to overcome these factors.

The population recruited in this study underwent cytological examination due to a variety of clinical indications; the most common being the presence of risk factors for EC, followed by abnormal imaging findings, abnormal vaginal bleeding and an abnormal Pap test result. In developed countries, EC has become the most common invasive malignancy of the female genital tract, exceeding cervical cancer in morbidity (35); the latter has been substantially limited by the implementation of well-organized screening programs with Pap smears, worldwide. In contrast, such screening methods do not exist for EC, where only medical history and clinical examination are ineffective, although mandatory, to give an accurate and prompt diagnosis of the disease. Of note, postmenopausal

Table V. *Results of the multivariate ordinal logistic regression analysis examining factors independently associated with difficulty score.*

Variables	Category or increment	Multivariate OR (95%CI)	*p*-Value
Menopausal status	Postmenopausal *vs*. Pre-/peri-menopausal	2.63 (1.52-4.56)	0.001
Previous invasive/surgical procedures in cervix	Yes *vs*. no	2.15 (1.10-4.24)	0.026

vaginal bleeding is an overestimated clinical symptom. Only 10% of women with the symptom are diagnosed with EC. Importantly, EC is curable when diagnosed early, with a 5-year survival rate to be more than 95% in Stage Ia (36), while, surgery alone can be curative. Thus, prompt diagnosis is linked with the lack of necessity of any type of adjuvant therapy, together with the absence of the related side-effects, whereas a great advantage in the patients' quality of life seems to be conferred.

A screening program for EC, would be of benefit not only to the patients' life itself, but also of a profitable practice for public health, since early diagnosis and treatment require for lower cost than that of treatment of advanced cases. There is currently no official program for screening and surveillance of women at increased risk of developing EC (37); on this basis, it has been suggested that endometrial liquid-based cytology could play a pivotal role in screening for EC in high-risk populations (38).

Despite the originality of the present findings, this study bears certain limitations. In our setting, Endogyn was the only method used for endometrial sampling, and was not compared with other methods described in the literature, such as the Tao Brush, which is figured with a low false-negative rate and easiness in use (26), the patented device called SAP-1 (24), the Novak curette (23) and the most widely used method, Pipelle (22). It would be, therefore, logical to anticipate further studies comparatively assessing various endometrial cytology sampling devices, especially implementing the herein documented risk factors. It is hard to predict how the use of other sampling devices would affect the results, as this study is the first on the field and no other comparable data have been published. On the other hand, a larger number of patients undergoing Endogyn could potentially have allowed the shifting of a trend implicating obesity as a risk factor for strenuousness (p=0.109, Table IV) to a significant finding. Indeed, a *post hoc* power calculation indicates that 660 patients would be needed for the achievement of 90% statistical power in the aforementioned comparison. Moreover, regarding the generalizability/external validity of the present findings, it should be stressed that this study was performed in a tertiary, referral Center on Caucasian women; it would be interesting to conduct such comparisons in other populations, such as Asian or Black participants.

In conclusion, this study highlights postmenopausal status and previous invasive/surgical procedures in the cervix as independent factors significantly associated with high strenuousness during endometrial cytology sampling. Increased vigilance and surveillance seems justified when sampling the endometrium of these two sub-groups of women. Adequately conducted studies seem necessary to further evaluate the findings of the present study in the context of other populations and sampling devices.

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