DOI:10.1111/cyt.12013

Diagnostic accuracy of liquid-based endometrial cytology in the evaluation of endometrial pathology in postmenopausal women

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Accepted for publication 3 August 2012

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Objective: The aim of this study was to compare liquid-based endometrial cytology with hysteroscopy and endometrial biopsy regarding its diagnostic accuracy in a series of postmenopausal women with abnormal uterine bleeding (AUB) or asymptomatic women with thickened endometrium assessed by transvaginal ultrasound as a screening procedure.

Methods: Inclusion criteria were: menopausal status; the presence of AUB and/or thickened endometrium assessed by ultrasound (cut-off 4 mm); a normal Papanicolaou (Pap) smear; and no adnexal pathology at ultrasound. Exclusion criteria were: previous endometrial pathology; and previous operative hysteroscopy. Of 768 postmenopausal women referred to our general gynaecology clinics, 121 fulfilled the inclusion criteria and were recruited to the trial. Twenty-one refused to participate. Cytological sampling was carried out by brushing the uterine cavity using the Endoflower device with no cervical dilation and the vial was processed using a ThinPrep® 2000 automated slide processor. The slides were stained using a Pap method.

Results: In 98 cases with histological biopsies, endometrial cytology detected five cases of endometrial carcinoma, 10 of atypical hyperplasia and 47 of non-atypical hyperplasia; 36 cases were negative. In two cases cytology was inadequate because of uterine cervical stenosis. Taking atypical hyperplasia or worse as a positive test and outcome, the diagnostic accuracy of the endometrial cytology was 93.5%, with a sensitivity of 92% and specificity of 95%, a positive predictive value of 73% and a negative predictive value of 99%. All the carcinomas were detected by cytology. Only 42% of women with a positive diagnosis were symptomatic. The cytological sampling was well tolerated by all patients. No complication was registered.

Conclusions: Liquid-based endometrial cytology can be considered an useful diagnostic method in the detection of endometrial pathology as a first-line approach, particularly if associated with transvaginal ultrasound.

Keywords: endometrial cytology, endometrial carcinoma, endometrial hyperplasia, histology, transvaginal ultrasound, liquid-based endometrial cytology

Introduction

Endometrial cancer is the fourth most common malignancy in women, and the most frequent gynaecological cancer in developed countries.[1,2] It frequently occurs in postmenopausal women, and abnormal uterine bleeding (AUB) is an early symptom. Only in the range between 0.07% and 0.6% are patients asymptomatic.[3–5] In about 10% of cases AUB is associated with endometrial cancer, but it can be caused by many other conditions, such as polyps, myomas, hormonal dysfunction and, most commonly in postmenopausal women, atrophy.[6,7]

Endometrial pathology can be identified using several methods, such as transvaginal ultrasound with

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or without Color-Doppler and 3-D analysis, hysteroscopy and endometrial biopsy, sonohysterography and the presence of endometrial cells in cervical cytology slides.[8–17] Transvaginal ultrasound is the most common currently used first-line diagnostic method because it is well tolerated, but its accuracy is based on the endometrial thickness alone.[11–13] Hysteroscopy with a biopsy is a second-line diagnostic tool, and is considered the gold standard in endometrial pathology detection.[18–20]

Traditionally, endometrial cytology was not considered sufficiently accurate in the detection of endometrial pathology, probably because of the common presence in the sample of confounding factors, such as blood and overlapping cells, which may hamper a correct diagnosis.[21] Recently, endometrial cytology has been re-evaluated with the introduction of liquid-based techniques that reduce obscuring factors, increasing the diagnostic accuracy.[22–24]

In the literature, there is a need for additional trials to evaluate the diagnostic accuracy of liquid-based endometrial cytology (LBEC) in the evaluation of endometrial pathology. The present study aimed to compare LBEC with hysteroscopy and endometrial biopsy to assess its diagnostic accuracy in a series of postmenopausal women with AUB and asymptomatic postmenopausal women with thickened endometrium assessed by ultrasound as a screening test.

Methods

The trial was performed at general gynaecology clinics in the Department of Surgery, Tor Vergata University Hospital, Rome. From March 2007 to 2010, all postmenopausal women with AUB or asymptomatic women with thickened endometrium assessed by transvaginal ultrasound as a screening procedure were considered eligible for the study. Inclusion criteria were: (1) postmenopausal status; (2) the presence of AUB and/or thickened endometrium assessed by US (cut-off, at 4 mm without hormonal replacement therapy [HRT], at 5 mm with HRT or tamoxifen); and (3) a normal Pap smear. Exclusion criteria were: (1) previous endometrial pathology; (2) previous operative hysteroscopy; and (3) adnexal pathology at ultrasound.

Of 768 postmenopausal women referred to our gynaecology clinics, 121 fulfilled the inclusion criteria, and were recruited for the trial (Table 1). Twenty-one refused to participate. Written informed consent was obtained from each patient before entry in the study.

The study was approved by the local ethics committee. There was no financial interest or any arrangement with the companies producing the instruments used in the study or with competitor companies. There also was no direct payment to the authors from any source for the purpose of financing the writing of the manuscript, nor were there any other financial connections, direct or indirect, or other situations that might raise the question of bias in the work.

Cytological sampling was carried out by the same gynaecologist by brushing the uterine cavity using the Endoflower device (RIMOS; Mirandola, Modena, Italy) with no cervical dilation (Figure 1). The device measures 3 mm in diameter and consists of a mandrel with an umbrella-shaped tip. Some micro-holes are sited on the three curved thin arms. The mandrel, sliding inside an outer sheath, allows non-traumatic sampling of the entire uterine cavity, including the fundal and cornual regions. After having collected the endometrial cells, the tip is retracted inside the introducer to prevent cervical contamination and the device is removed. The umbrella-shaped tip is then immersed in the Cytolyt® vial (formerly Cytyc Corporation [now Hologic®] Boxborough, MA, USA), where it is shaken to allow the cells to release. The sample is centrifuged and the pellet containing the cells is transferred into a vial containing PreservCyt® (formerly Cytyc Corporation). With a succession of centrifugation and suspension to obtain mucolysis and hemolysis, blood and mucus are separated from the endometrial cells. At the end, the vial is processed using ThinPrep® 2000 automated slide processor

Table 1. Distribution of patients according to inclusion criteria and age

Inclusion criteria	Endometrial thickness (mm) mean ± SD (range)	Number of patients	Age (years) mean ± SD (range)
Thickened endometrium	8.08 ± 3.85 (5–23)	70	62 ± 7.27 (47–81)
Thickened endometrium + AUB	8.00 ± 2.00 (5–11)	12	61 ± 7.70 (50–71)
AUB	2.27 ± 1.02 (1–4)	18	62 ± 9.22 (41–77)

AUB, abnormal uterine bleeding; SD, standard deviation.

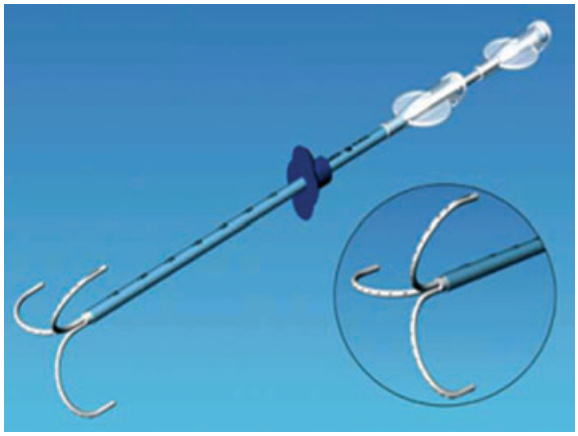

Figure 1. Endoflower sampling device.

(formerly Cytyc Corporation) and the slides stained with a Papanicolaou (Pap) method.

Office hysteroscopy was performed by the same gynaecologist using a 2.7-mm optic with saline solution distension after the cytological sampling. An endometrial biopsy was carried out using the Endoram device (RIMOS; Mirandola) measuring 3.8 mm in diameter. Endometrial samples were routinely fixed in neutral buffered formol, embedded in paraffin, and stained with haematoxylin and eosin.

The cytological and histological samplings were examined by the same pathologist. A numerical code was randomly assigned to each cytological and histological sample, and the pathologist was blinded to the correspondence between the code numbers and the cases examined. The assessments were made independently of each other, with the pathologist blinded to the result of the other assessment. The cytological criteria used in the cellular interpretation were according to existing techniques.[22,25,26] The cytological findings were subdivided into four categories: negative, non-atypical hyperplasia, atypical hyperplasia and neoplasia (Figure 2a–d). Negative and non-atypical hyperplasia were considered as negative, and atypical hyperplasia and neoplasia as positive cytological results. The cytological findings were correlated with the histological results at hysteroscopy, which were considered as the gold standard; atypical hyperplasia or worse was taken as a positive outcome.

Statistical analysis was performed using the Statistical Program/SPSS for Windows, version 10 (SPSS Inc., Chicago, IL, USA). A double access table was created to evaluate the sensitivity of cytology (true positive/all positive biopsies), specificity (true negative/all negative biopsies), the positive predictive value (PPV) (true positive/all positive cytology results), the negative predictive value (NPV) (true negative/all negative cytology results) and diagnostic accuracy (true positive plus true negative/true and false positive plus true and false negative).

Results

The distribution of patients according to inclusion criteria is shown in Table 1. The median age of women was 62 ± 7.63 years, median age at last menses 50 ± 3.87 years. Their median number of deliveries and miscarriages was 2 ± 1.04 and 0.71 ± 1.18, respectively. Some women had risk factors for endometrial cancer, such as diabetes, hypertension, smoking, HRT, Tamoxifen therapy and obesity (Table 2), whereas 57 did not have any risk

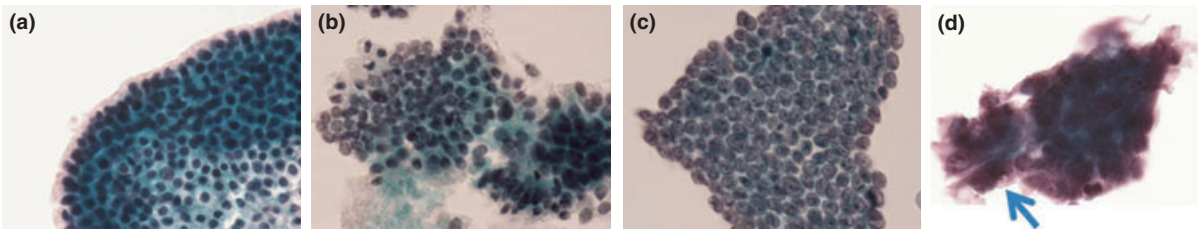

Figure 2. Liquid-based endometrial cytology (Papanicolaou × 60 objective). (a) Normal endometrium: glandular cells with small, round, dense, pyknotic nuclei and scant cytoplasm. (b) Non-atypical endometrial hyperplasia: glandular cells characterized by apparent nuclear crowding, variation in the nuclear size with small nucleoli and evenly granular chromatin. (c) Atypical endometrial hyperplasia: glandular cells with enlarged round or ovoid nuclei, frequent nucleoli, dense irregular chromatin, nuclear overlapping and scant cytoplasm. (d) Endometrial carcinoma: sheets of glands with crowded cells, enlarged nuclei with frequent prominent nucleoli and an abnormal mitosis (arrow).

Table 2. Risk factors of patients

Risk factors	Thickened endometrium	Thickened endometrium + AUB	AUB	Number of patients	%
Diabetes	1	0	1	2	2
HRT	2	0	0	2	2
Hypertension	10	1	1	12	12
Smoking	4	1	0	5	5
Tamoxifen	9	0	1	10	10
Diabetes + hypertension	0	0	2	2	2
Smoking + hypertension	3	1	0	4	4
Tamoxifen + hypertension	1	0	0	1	1
Tamoxifen + smoking	2	0	0	2	2
Smoking + obesity	0	1	0	1	1
Hypertension + obesity	1	1	0	2	2
None	37	7	13	57	57
Total	70	12	18	100	100

HRT, hormone replacement therapy; AUB, abnormal uterine bleeding.

Table 3. Correlation between histological and cytological results

	Cytology			
Histology	Negative (n = 36)	Non-atypical hyperplasia (n = 47)	Atypical hyperplasia (n = 10)	Neoplasia (n = 5)
Negative or atrophy (n = 38)	35		3	
Non-atypical hyperplasia (n = 9)		9		
Endometrial polyp (n = 38)		37		1
Submucosal leiomyoma (n = 1)		1		
Total negative or non-atypical hyperplasia (n = 86)				
Simple or complex atypical hyperplasia (n = 8)	1		7	
Neoplasia (n = 4)				4
Total atypical hyperplasia or neoplasia (n = 12)				

factor. The latter were tested because they had AUB and/or thickened endometrium assessed by transvaginal ultrasound.

A correlation between cytological results and histological diagnosis is illustrated in Table 3. In 98 cases, endometrial cytology diagnosed five cases of endometrial cancer, 10 of atypical hyperplasia and 47 of non-atypical hyperplasia; 36 cases were negative. In two cases cytology was inadequate because of uterine cervical stenosis: office hysteroscopy with endometrial biopsy was performed, and histological diagnosis was atrophy in one patient, and an endometrial polyp in the other.

Table 4. Diagnostic accuracy of the liquid-based endometrial cytology in the detection of atypical hyperplasia or worse as test and outcome positivity

Endometrial cytology	%	95% CI
Sensitivity	92	75–100
Specificity	95	90–100
Diagnostic accuracy	93	76–100
Positive predictive value	73	67–80
Negative predictive value	99	81–100

CI, confidence interval.

Histological diagnosis identified endometrial cancer in four patients, atypical hyperplasia in eight, endometrial polyps in 38, non-atypical hyperplasia in nine, submucousal myoma in one patient and no pathology in 38. In Table 4, the diagnostic accuracy of LBEC is reported. There was one false-negative and four false-positive cytology results (three false positive if all degrees of abnormality are taken as positive). All the carcinomas had positive cytology. Among all the positive diagnoses (atypical hyperplasia or worse), only 42% of women were symptomatic.

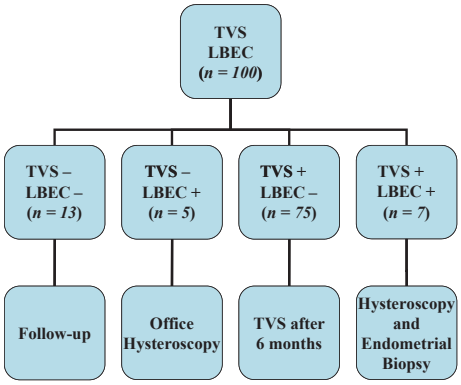

Figure 3. Diagnostic work up of postmenopausal women with (n = 30) and without (n = 70) abnormal uterine bleeding. TVS, transvaginal ultrasound; LBEC, liquid-based endometrial cytology.

The flow chart in Figure 3 demonstrates the clinical management based on the ultrasound and cytology results of women in this study.

Discussion

Endometrial cancer is the most frequent form of gynaecological neoplasia, but there is no reliable screening test for its early detection. Currently, transvaginal ultrasound is the first-line endometrial investigation, even although its diagnostic accuracy is only based on the endometrial thickness in relation to the cut-off considered.

With an endometrial thickness cut-off from 3 to 5 mm, sensitivity goes from 90% to 100% and the NPV from 90% to 100%, whereas specificity decreases from 78% to 60% and the PPV from 69% to 4%.[11–13] When an endometrial thickening is detected by ultrasound, it is necessary to have access to office hysteroscopy with endometrial biopsy, which is considered the gold standard.

Traditional endometrial smears have not found a place in endometrial diagnostic workup because of their low diagnostic accuracy, with a sensitivity of about 78%, specificity of 95%, PPV of 56% and NPV of 98%.[21] In spite of this, in Japan since 1987, conventional endometrial cytology has become a routine method for the initial examination of endometrial lesions.[27]

In order to improve the diagnostic accuracy of endometrial cytology, the thin layer method was proposed for the detection of endometrial disorders. In the first study published in 2003, Garcia *et al.*[28] performed endometrial thin layer cytology in 203 symptomatic women reporting a specificity of 96% and sensitivity of 78% with an inadequate rate of 15%. In the same year, Buccoliero *et al.*[29] reported a cyto-histological concordance of 98%, and an inadequate rate of 18% in a population of 162 women before hysterectomy (55 symptomatic and 107 asymptomatic with prolapsed uterus). In 2007, the same authors performed liquid-based endometrial cytology in a population of 917, symptomatic and asymptomatic, pre- and postmenopausal women. They reported a sensitivity of 96%, specificity of 98%, PPV of 86% and NPV of 99%. They emphasized that cytology provided sufficient material more frequently than a biopsy, and the difference was statistically significant.[25] In the same year, they performed liquid-based endometrial cytology in 320 asymptomatic women reporting a sensitivity of 94%, specificity of 95%, PPV of 80% and NPV of 99%. Cytological sample was adequate more often than endometrial biopsy.[30]

The findings of our study support those results, having obtained a sensitivity of 92%, specificity of 95%, PPV of 73% and NPV of 99%. It is important to underline that all the cancers had positive cytology. The four false-positive results and the unique false-negative finding were registered in the early stage of the study, when both the gynaecologist and the pathologist had to improve the technique of endometrial sampling and its cytopathological interpretation. The main reason probably consisted of the presence of cervical cells, a problem solved by cleaning the tip of the device with a gauze.

An additional improvement to LBEC in the evaluation of endometrial pathology could be obtained using immunocytochemical analysis with PTEN, β-catenin, and p53.[31] Another possible application could result from the sampling obtained using a cytological device that provides cytology slides by means of membrane filtration and microbiopsies embedded in paraffin. Membrane-filtered cytology slides seem to be comparable to liquid-based cytology slides, but cheaper, and the sampler adequacy is still better than histology.[32]

On the basis of our results, and considering that only the 42% of women with a positive diagnosis (atypical hyperplasia or worse) were symptomatic, we believe that liquid-based endometrial cytology can be considered an useful diagnostic method in the detection of endometrial pathology as a first-line approach, particularly if associated with transvaginal ultrasound. Nevertheless, further studies are necessary to confirm its diagnostic accuracy as acceptable, and to

investigate whether immunocytochemistry could significantly improve the diagnostic accuracy, so reducing the number of more expensive and invasive diagnostic tools.

If the use of diagnostic technique is to spread, it will probably be necessary to create a classification of the cytological results to improve the exchange of information between the clinician and pathologist. For this purpose, a Japanese group proposed a reporting format similar to the Bethesda System.[27] They proposed considering the specimen adequacy as 'satisfactory for evaluation', 'less than optimal' and 'unsatisfactory for evaluation'. The results were categorized into four groups: '(1) negative; (2) atypical endometrial cells of undetermined significance (AEC-US), suspicious for benign endometrial disease or simple endometrial hyperplasia (endometrial biopsy is not recommended); (3) atypical endometrial cells encompassing the spectrum of precursors to endometrial tumor (AEC-PEMT), suspicious for complex hyperplasia, simple or complex atypical hyperplasia, adenocarcinoma *in situ* (biopsy is recommended); and (4) positive: suspicious for a malignant tumor'.[27] The value of this classification and the development of other classification systems should be subject of further clinical trials in order to identify an optimal categorization of endometrial pathology.

In conclusion, it is possible for liquid-based endometrial cytology together with transvaginal ultrasound to be an initial step in the diagnostic workup of AUB in postmenopausal women. If both methods are negative, women return to routine follow-up. If cytology alone is positive, women are offered office hysteroscopy. If ultrasound alone is positive, a repeat in 6 months is recommended. If both ultrasound and cytology are positive, women will undergo hysteroscopy with an endometrial biopsy.

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