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Liquid-based endometrial cytology: cyto-histological correlation in a population of 917 women

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Objective: Liquid-based cytology, because of its capacity to reduce the obscuring factors and to provide thin-layer specimens, represents an opportunity to reevaluate endometrial cytology. In order to assess the utility of the liquid-based method in endometrial diagnosis, we evaluated its accuracy in comparison with histology.
Methods: Nine hundred and seventeen women scheduled for hysteroscopy were enrolled in the study. After providing informed consent, all the women proceeded sequentially to hysteroscopy, endometrial cytology and then biopsy endometrial sampling.
Results: Cyto-histological correlations were possible in 519 cases (57%): in 361 (39%) cases the biopsy was inadequate, in 15 (2%) the cytology was inadequate, and in 22 (2%) both were inadequate. At biopsy 25 (3%) women had adenocarcinoma, 5 (1%) had adenomatous atypical hyperplasia and 21 (2%) had simple non atypical hyperplasia. At cytology two adenocarcinomas and one adenomatous atypical hyperplasia were underrated as atypical hyperplasias and as non-atypical hyperplasia; two simple non-atypical hyperplasias were reported as negative; and eight cases were false positive (non-atypical hyperplasia at cytology, negative at biopsy). In our population, the cytology provided sufficient material more often than biopsy ($P < 0.04$). Sensitivity was estimated at 96%, specificity at 98%, positive predictive value at 86% and negative predictive value at 99%.
Conclusions: We concluded that endometrial cytology may be an efficient diagnostic method. It could be applied to selected patients solely or in association with ultrasonography. The combination of these two noninvasive procedures may improve their diagnostic accuracy and reduce unnecessary hysteroscopies, thereby producing benefits for women and society.

Keywords: endometrial neoplasms, uterine neoplasms, cytodiagnosis, cytological techniques, ThinPrep, LBC, liquid-based cytology

Introduction

Endometrial adenocarcinoma ranks fifth in incidence among malignancies in women, and it is the most frequent malignancy of the female genital tract in developed countries. The majority of the cases are sporadic whereas about 10% are hereditary. Most important among the latter, is the autosomal dominantly inherited non-polyposis colorectal cancer caused by mutation of a DNA mismatch repair gene that determines constitutive microsatellite instability and Cowden syndrome in patients with germ line PTEN inactivation.[1–10]

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Two subtypes of endometrial carcinoma, named type I and type II, have been described on the basis of their different age of development, aetiopathogenesis, histopathological features and prognosis. Type I adenocarcinoma, which accounts for most cases (approximately 80%), occurs in peri-menopausal women, is oestrogen dependent, more often well differentiated and endometrioid, and has a favourable behaviour with appropriate therapy. Conversely, the rare type II endometrial adenocarcinoma affects older postmenopausal women, is oestrogen independent, predominantly of serous papillary or clear cell histotype, and has a worse prognosis with a high incidence of upper abdominal metastases and dissemination. Type I adenocarcinoma is frequently preceded by endometrial hyperplasia whereas type II is not. Indeed, the precursor of serous papillary endometrial carcinoma is serous endometrial intraepithelial carcinoma (also named surface serous carcinoma or minimal uterine serous carcinoma) which frequently arises on atrophic endometrium. Moreover, type I carcinomas are associated with mutations in the K-*ras* proto-oncogene, and in the PTEN tumour suppressor gene, and often show microsatellite instability, but do not usually have mutations in the p53 tumour suppressor gene. By contrast, type II carcinomas show frequent p53 mutations, but rarely have microsatellite instability, K-*ras* or PTEN mutations.[1, 8, 9, 11–14]

Most women with endometrial cancer are diagnosed at an early stage as vaginal bleeding is an early, even if nonspecific, presenting symptom.[1, 15, 16] Unlike cervical carcinoma, no mass screening programmes for the early detection of endometrial carcinoma have been organized. The early presenting symptoms and the good prognosis of the majority of endometrial adenocarcinomas may explain the limited interest in screening this neoplasm in spite of its high frequency and the existence of morphological precursors. On the other hand, there has not been a test comparable to cervicovaginal cytology for tolerability, sensitivity, specificity and low cost.

Endometrial cytology has been hampered in its dissemination by difficulty in its interpretation due to the common presence of excess blood and overlapping cells. In addition, the physiology of the endometrium may determine difficulties in the cytopathological interpretation of the specimens, especially by non-pathologists.[17–20]

Liquid-based cytology represents an opportunity to re-evaluate endometrial cytology; an increasing interest in it is demonstrated by a number of articles which report interesting results in terms of diagnostic accuracy.[21–23]

In order to assess the utility of liquid-based cytology in endometrial diagnosis we evaluated the accuracy of liquid-based endometrial cytology compared with the histological diagnosis in a group of 917 women scheduled for hysteroscopy.

Patients and methods

The patients included in this study were 917 consecutive women scheduled for hysteroscopy in which the absence of cervical stenosis made the investigation possible. After providing informed consent, all the women proceeded sequentially to hysteroscopy, endometrial cytology and biopsy endometrial sampling.

Their median age was 52 years (range 23–89). In the majority of the cases, 663 women (72%), hysteroscopy was required for thickened endometrium (>4 mm) as evaluated by transvaginal ultrasonography; 345 (38%) women were referred for abnormal uterine bleeding; 74 (8%) were tamoxifen users.

Cytological sampling was performed using the Endoflower device (RI-MOS; Mirandola, Modena, Italy) (Figure 1) made of a radio-opaque technopolymer material measuring 3 mm in diameter. It consists of a mandrel with a shaped tip containing micro holes on curved thin arms that slide inside an outer sheath. An adjustable positioner is placed on the outer sheath to determine the correct insertion depth. Before the introduction of the device into the uterus, the umbrella-shaped tip was withdrawn inside the introducer. Once inside the uterine cavity, the umbrella-shaped tip was released and rotated clockwise and counter-clockwise.

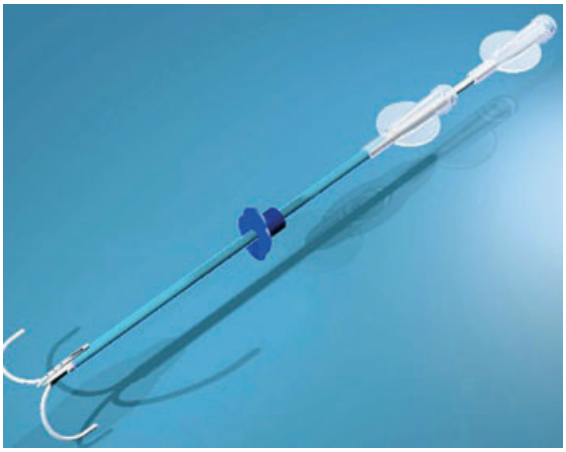

Figure 1. Endoflower device.

After the collection of endometrial material, the tip was withdrawn inside the introducer to prevent cervical contamination and the device removed. Outside the uterus, the device was cleaned with gauze to remove cervical cell contamination and then the umbrella-shaped tip was exposed and immersed in the Cytolyt® (Cytyc Corporation, Boxborough, MA, USA) vial and vigorously rotated. The device was removed from the vial and the vial was labelled with the appropriate patient information and transported to the Department of Pathology where the samples were processed and the diagnoses made.

After centrifugation (300 *g* for 5 minutes), the pellet containing the cells was transferred into a vial containing PreservCyt® (Cytyc Corporation). PreservCyt® mildly fixes the cells within 10–15 minutes so preserving them for at least 3 weeks at room temperature. Blood and mucus were eliminated by means of washing through the succession of centrifugation and resuspension in N-acetyl-l-cisteine (mucolysis; before fixation in PreservCyt®) and/or acetic acid (haemolysis; after fixation in PreservCyt®). The vial was inserted into the ThinPrep 2000 automated slide processor (Cytyc Corporation), which, in about 1 minute and 30 seconds, prepares a smear in a thin layer within a microscopic field measuring 20 mm in greatest dimension. The slides were stained with routine Papanicolaou stain.

Histological sampling was performed using the Endoram device (RI-MOS). Endometrial samples were routinely fixed in neutral buffered formol, embedded in paraffin and stained with haematoxylin and eosin.

Cytological and histological diagnoses were executed blindly by two cyto-histo-gynaecopathologists (A.M.B. and G.L.T.). In cases of discordant diagnosis both pathologists reviewed the case together and reached an agreement on the diagnosis. The slides were considered inadequate when there were less than five evaluable endometrial clusters (endometrial cytology) or severe fragmentation or scarcity of the endometrial tissue (endometrial biopsy). If the first cytological or histological slide was inadequate a second slide was prepared. When the second one was also unsatisfactory the diagnosis was considered as 'inadequate'.

The cytological diagnosis was given according to the criteria previously reported.[24] We considered four categories: normal (grouping proliferative, secretory and atrophic endometrium; Figures 2–4), non-atypical hyperplasia (Figure 5), atypical hyperplasia and carcinoma (Figure 6a–d), on the basis of the architectural and cytological features of the endometrial clusters, considering all anamnestic and clinical information. Table 1 outlines the main diagnostic criteria used. Cytological specimens with occasional endometrial clusters showing non-atypical hyperplastic features were considered negative when hysteroscopy and/or ultrasonography diagnosed an endometrial polyp.

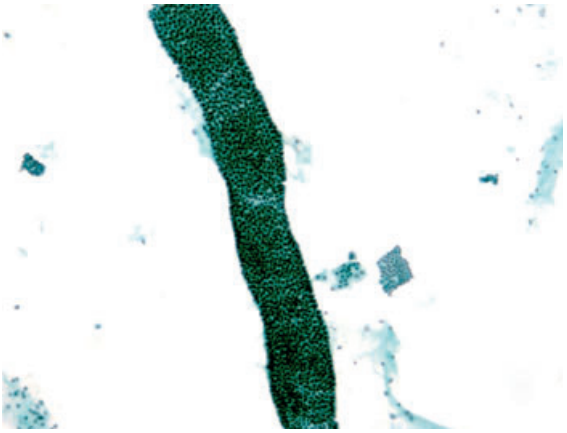

Figure 2. Proliferative endometrium: three-dimensional cylindrical endometrial cluster formed by isomorphic cells with scant cytoplasm and regular nuclei.

The histological diagnosis conformed to the World Health Organization criteria.[1]

Due to the small number of pathological specimens, statistical analyses were performed by categorizing the cases as non-pathological and pathological

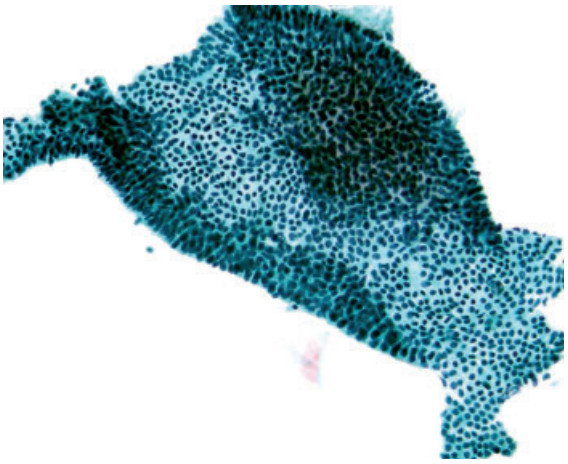

Figure 3. Secretory endometrium: endometrial placards formed by isomorphic cells with large clear cytoplasm and regular nuclei.

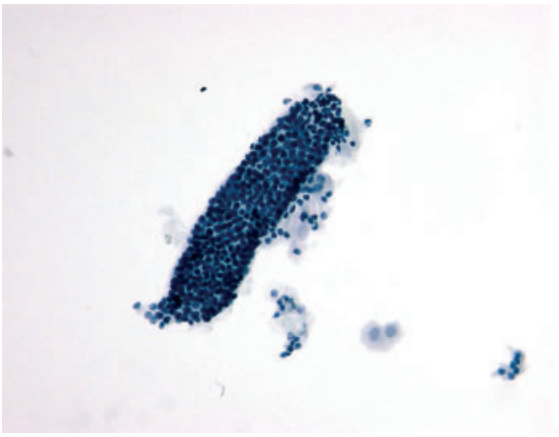

Figure 4. Atrophic endometrium: small three-dimensional endometrial cluster formed by isomorphic cells, with scant cytoplasm and hyperchromatic regular nuclei.

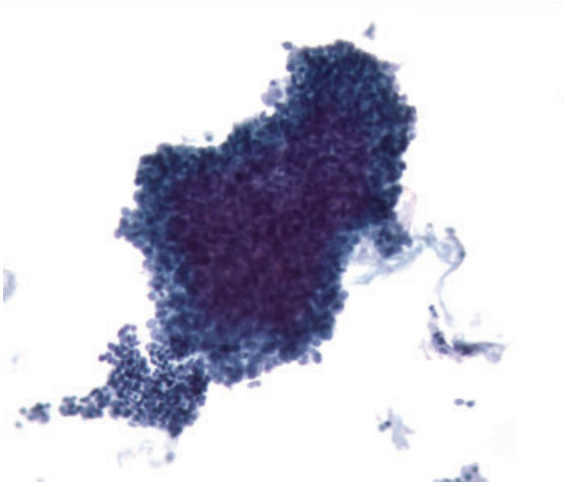

Figure 5. Non-atypical hyperplasia: wide three-dimensional cluster with considerable cellular crowding and architectural disorder.

(hyperplasia, atypical hyperplasia and carcinoma). The sensitivity was calculated by dividing the true pathological cases diagnosed by endometrial cytology by the total number of patients with endometrial pathology and multiplying by 100. The specificity was calculated by dividing the number of true negative cases diagnosed by endometrial cytology by the total number of women who did not have endometrial disease and multiplying by 100. The positive predictive value was calculated by dividing the true pathological cases by the total number of true positive cytological specimens and the false-positive cases and multiplying by 100. The negative

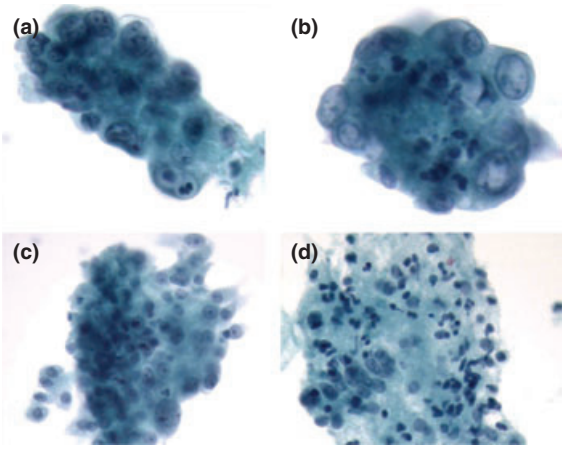

Figure 6. Endometrial adenocarcinoma: small endometrial clusters (a–c) with papillary configuration (b) in a inflammatory-necrotic background (d).

predictive value was calculated by dividing the true negative cases by the total of true negative and the false-negative cytological specimens and multiplying by 100. The chi-squared test was used to compare the number of unsatisfactory cytological specimens with that of endometrial biopsies. Statistical significance was judged as $P < 0.04$. Data analysis was performed using the Glaz SA 3.03 Version statistical package (Mc Graw-Hill, New York, NY, USA).

Results

In 815 cases (89%) hysteroscopy did not detect features of hyperplasia or neoplasia.

Thirty-seven (4%) cytologies and 383 biopsies (42%) were inadequate. Of the 383 inadequate endometrial biopsies, 350 (38%) were considered inadequate by the gynaecologists because of the scarcity of the sampled tissue and no specimens were transported to the pathologists; the remaining 33 (4%) inadequate cases were judged inadequate by pathologists during histopathological evaluation.

In 361 (39%) cases only the biopsy was inadequate; in 15 (2%) only the cytology was inadequate; and in 22 (2%) cases both the biopsy and the cytology were inadequate.

Cyto-histological correlation was possible in the remaining 519 cases (57%). The majority of inadequate cases (91%) were women aged older than 50.

Evaluation of the biopsies determined that 25 (3%) women had adenocarcinoma, five (1%) had adenomatous atypical hyperplasia and 21 (2%) had simple

Table 1. Main diagnostic criteria

	Endometrial Cells						Background
	Epithelial cells					Stromal cells	
	Quantity	Architecture	Polarity	Cytoplasm	Nucleus		
Proliferative	Abundant	Three-dimensional cylindrical clusters	Preserved	Scant	Isomorphic, finely granular chromatin, small or absent nucleoli	Spindle-shaped	Clean
Secretory	Abundant	Wide three-dimensional cylindrical clusters or bi-dimensional placards	Preserved	Large	Isomorphic, dispersed chromatin, small or absent nucleoli	Epithelioid	Moderately inflammatory (late secretory)
Atrophic	Scant	Small three-dimensional clusters	Preserved	Scant	Small, isomorphic, dense chromatin, small or absent nucleoli	Abundant, spindle-shaped	Clean, multinucleated histiocytes
Non-atypical hyperplasia	Abundant	Wide three-dimensional clusters with considerable cellular crowding	Architectural disorder	Scant	Isomorphic, finely granular chromatin, small or absent nucleoli	Spindle-shaped	Moderately inflammatory
Atypical hyperplasia	Abundant	Wide three-dimensional clusters with variable cellular crowding	Architectural disorder	Visible	Variably pleomorphic, granular chromatin, presence of nucleoli	Scant, spindle-shaped	Moderately inflammatory
Carcinoma	Abundant	Endometrial clusters with variable dimensions and cellular crowding; loss of cellular cohesion	Architectural disorder	Visible	Pleomorphic, coarsely granular chromatin, presence of nucleoli and/or macronucleoli	Scant, spindle-shaped	Inflammatory

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non atypical hyperplasia. Endometrial cytology diagnosed 24 endometrial carcinoma cases, six hyperplastic with atypia cases and 48 hyperplastic without atypia cases. One endometrial adenocarcinoma, occurring in a woman on tamoxifen, was initially only detected by endometrial cytology while the biopsy was inadequate (as judged by the gynaecologist). The cytological diagnosis was confirmed by a subsequent endometrial curettage (Table 2).

In the series of 519 cases in which both endometrial biopsy and cytology were adequate, endometrial cytology recognized 23 endometrial carcinoma cases, six hyperplastic with atypia cases and 28 hyperplastic without atypia cases (Table 3). Two endometrial adenocarcinomas and one atypical hyperplasia were underrated by endometrial cytology and resulted as atypical hyperplasias and as non-atypical hyperplasia respectively. Two simple non-atypical hyperplasias were reported as negative by cytology. Eight cases were false positive by cytology (non-atypical hyperplasias by cytology, negative on biopsy).

When we categorized the cases studied as non-pathological and pathological, cyto-histological concordance was 98%; sensitivity was estimated at 96%, specificity at 98%, positive predictive value at 86% and negative predictive value at 99%. Endometrial cytology provided sufficient material for the diagnosis significantly more often than endometrial biopsy ($P < 0.04$).

Discussion

The incidence of endometrial carcinoma has increased and currently represents the most prevalent malignant gynaecological tumour. This increase has primarily been attributed to the increase in the average life expectancy of women, the increase in the incidence of risk factors such as obesity, low parity, hypertension and diabetes, and also to the reduction in the incidence of invasive cervical carcinoma. Furthermore, the frequent administration of exogenous oestrogens, particularly without the differentiating effects of progestens, and of tamoxifen (a drug having an oestrogenic effect on the female genital tract often used in women with breast cancer) have been identified as additional factors responsible for the increased incidence of endometrial adenocarcinoma.[1, 2, 7–10, 25–27] The prevention, detection of the pre-neoplastic conditions, early diagnosis of neoplastic lesions and appropriate treatment are efficient anti-cancer strategies.

Thin-layer cytology may represent a useful method for detecting endometrial pre-neoplastic conditions

Table 2. Histological and cytological results (917 women)

	Histology, *n* (%)	Cytology, *n* (%)
Non-pathological	483 (53)	802 (88)
Pathological	51 (5) (25 adenocarcinomas, 5 adenomatous atypical hyperplasias, 21 simple non-atypical hyperplasias)	78 (8) (24* adenocarcinomas, 6 atypical hyperplasias, 48 non-atypical hyperplasias)
Inadequate	383 (42)	37 (4)
Total	917 (100)	917 (100)

*Twenty-three adenocarcinomas were diagnosed both by cytology and on biopsy; one was detected by cytology only (endometrial biopsy did not obtain sufficient diagnostic tissue as judged by gynaecologist) and subsequently confirmed by an endometrial curettage.

Table 3. Histological and cytological results (519 women in which both biopsy and cytology were adequate)

	Histology, *n* (%)	Cytology, *n* (%)
Non-pathological	468 (90)	462 (89)
Pathological	51 (10) (25 adenocarcinomas, 5 adenomatous atypical hyperplasias, 21 simple non-atypical hyperplasias)	57 (11) (23 adenocarcinomas, 6 atypical hyperplasias, 28 non-atypical hyperplasias)
Total	519 (100)	519 (100)

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(hyperplasias or serous endometrial intraepithelial carcinoma) and neoplastic lesions at an early stage. Even if abnormal uterine bleeding, particularly in the postmenopausal age, is generally regarded both by clinicians and women as an alarming and serious symptom, only in a minority of the cases is a precancerous or cancerous condition detected. Instead, the more commonly encountered cause of uterine bleeding is atrophic endometrium. Iatrakis *et al.*[16] concluded that, in a group of 628 patients with a median age of 52 years, atrophic endometrium was found in 83% of the cases and carcinoma of the endometrium in only 11%. A similar percentage was reported by Choo *et al.*[15] which retrieved atrophic endometrium and endometrial adenocarcinoma in 82% and 7% respectively. Only a small number of endometrial carcinomas, ranged between 0.07% and 0.6%,[28–31] are incidentally diagnosed in asymptomatic patients. This last percentage is higher in women with risk factors. Particularly, Grönroos *et al.*[32] estimated the incidence of invasive or pre-invasive endometrial lesions as 6.3% in a group of 597 asymptomatic diabetic women.

In this context, the relatively low incidence of neoplastic conditions in patients with postmenopausal bleeding may discourage the use of an invasive diagnostic procedure initially and the low prevalence rate of the disease among asymptomatic women without risk factors dissuades from screening these women. However, the presence of risk factors may require careful surveillance of symptomatic and asymptomatic women.

Several diagnostic procedures are available in the investigation of the endometrium. Hysteroscopy, endometrial biopsy, and dilatation and curettage are efficient diagnostic methods. The optimal circumstance is an endometrial biopsy under hysteroscopic control. Nevertheless, these procedures are not tolerated well despite the introduction of mini-hysteroscopes and flexible hysteroscopes which have reduced the discomfort produced by traditional hysteroscopy.[33, 34] In addition, endometrial biopsy, particularly in postmenopausal women, may not obtain endometrial tissue sufficient for histopathological evaluation. In our previous study of 107 asymptomatic postmenopausal women with thin endometrium (<4 mm), biopsy gave sufficient material for the diagnosis in only 24% of the cases.[22] Analogously, Elsandabesee and Greenwood[35] estimated that there is a 27% probability of getting an adequate endometrial sample in women with thin endometrium and Bakour *et al.*[36] affirmed that in cases with atrophic endometrium and/or focal lesion only minimal tissue can be obtained.

Transvaginal ultrasonography is a noninvasive method but its specificity is often low, particularly in tamoxifen users where the endometrial thickness is frequently overestimated because of oedema.[37] A recent meta-analysis of the diagnostic accuracy of endometrial thickness measurements by transvaginal or transabdominal ultrasound involving 9,031 women with postmenopausal bleeding and covering 57 separate studies reported that using a ≤5 mm cut-off level, a positive test raised the probability of carcinoma from 14.0% to 31.3% while a negative test reduced it to 2.5%. These results persuaded the authors to conclude that ultrasonography has limited predictive value for endometrial hyperplasia or carcinoma.[38]

Regarding traditional endometrial cytology, despite several encouraging results having reported sensitivity and specificity reaching 96%,[39–43] its acceptance has been hampered as a consequence of technical and diagnostic difficulties. In 1955, Hecht[44] warned of the danger of the use of the endometrial cytology and several years later, in 1990, Caubel *et al.*[45] further supported this warning, advising that the endometrial cytological diagnosis should always be confirmed by a histological diagnosis.

Endometrial cytology should be reconsidered as a diagnostic tool when coupled with liquid-based processing. The characteristics of this method, reduction in the obscuring factors, distribution of the cells on a thin layer, possibility of obtaining more than one slide available for further investigation, i.e. immunohistochemistry, may really represent an interesting opportunity on condition that an appropriate device is utilized, the diagnostic interpretation of the specimens is delegated to pathologists or to people skilled in endometrial physio-patho-morphology, and that, in cyclic women, the timing of the sampling is correct (secretory phase). In particular, the correct sampling timing is important due to the possible problematic differential diagnoses between proliferative endometrium and non-atypical hyperplastic endometrium.

Some recent studies emphasized the diagnostic potentiality of endometrial thin-layer cytology. In 2003, Garcia *et al.*[21] performed a prospective study of 103 symptomatic women and reported a very good specificity (96%), good (78%) sensitivity and a

low (15%) inadequate rate (lower than endometrial biopsy, calculated at 26%). In the same year, our group[22] documented a cyto-histological concordance of 98% and a low inadequate rate (18%) in a population of 162 women. In 2005, Papaefthimiou *et al.*[23] reported that liquid-based endometrial cytology allows for the application of common diagnostic criteria, therefore making possible a nearly perfect interobserver and intraobserver agreement. The low percentage of inadequate specimens, the high sensitivity, specificity, and positive and negative predictive values seen in our present study support these findings.

The high inadequate rate of endometrial biopsies in our collection may be related to the predominance of peri-postmenopausal women (91% of the inadequate cases were women older than 50 years) and of negative cases (Tables 2 and 3). On the other hand, the presence of a case of adenocarcinoma undiagnosed by biopsy but detected by cytology only emphasizes that inadequate biopsy, particularly in symptomatic women, does not exclude an endometrial pathology.[46]

In conclusion, we consider endometrial cytology an efficient diagnostic method. It could be applied to selected patients solely or in association with transvaginal ultrasonography. The combination of these procedures may improve their diagnostic accuracy[47] and reduce unnecessary hysteroscopies for women as well as provide social benefits as a consequence of the reduction of a more invasive and more expensive diagnostic procedure.

References

1. Tavassoli FA, Devilee P. *Tumours of the Breast and Female Genital Organs. Pathology and Genetics*. World Health Organization Classification of Tumours. Lyon, France: IARC Press; 2003.
2. Jick H, Walker AM, Rothman KJ. The epidemic of endometrial cancer: a commentary. *Am J Public Health* 1980;**70**:264.
3. Mecklin JP, Jarvinen HJ. Tumor spectrum in cancer family syndrome (hereditary nonpolyposis colorectal cancer). *Cancer* 1991;**68**:1109–12.
4. Esteller M, Levine R, Baylin SB, Ellenson LH, Herman JG. MLH1 promoter hypermethylation is associated with the microsatellite instability phenotype in sporadic endometrial carcinomas. *Oncogene* 1998;**17**:2413–7.
5. Mutter GL. Pten a protean tumor suppressor. *Am J Pathol* 2001;**158**:1895–8.
6. Dove-Edwin I, Boks D, Goff S *et al.* The outcome of endometrial carcinoma surveillance by ultrasound scan in women at risk of hereditary non polyposis colorectal carcinoma and familial colorectal carcinoma. *Cancer* 2002;**94**:1708–12.
7. Paley PJ. Screening for the major malignancies affecting women: current guidelines. *Am J Obstet Gynecol* 2001;**184**:1021–30.
8. Kaaks R, Lukanova A, Kurzer MS. Obesity, endogenous hormones, and endometrial cancer risk: a synthetic review. *Cancer Epidemiol Biomarkers Prev* 2002;**11**:1531–43.
9. Münstedt K, Grant P, Woenckhaus J, Roth G, Tinneberg HR. Cancer of the endometrium: current aspects of diagnostics and treatment. *World J Surg Oncol* 2004;**21**:24.
10. Bray F, Dos Santos Silva I, Moller H, Weiderpass E. Endometrial cancer incidence trends in Europe: underlying determinants and prospect for prevention. *Cancer Epidemiol Biomarkers Prev* 2005;**14**:1132–42.
11. Bokhman JV. Two pathogenetic types of endometrial carcinoma. *Gynecol Oncol* 1983;**15**:10–7.
12. Sherman ME. Theories of endometrial carcinogenesis: a multidisciplinary approach. *Mod Pathol* 2000;**13**:295–308.
13. Koul A, Willen R, Bendahl PO, Nilbert M, Borg A. Distinct sets of gene alterations in endometrial carcinoma implicate alternate modes of tumorigenesis. *Cancer* 2002;**94**:2369–79.
14. Hui P, Kelly M, O'Malley DM, Tavassoli F, Schwartz PE. Minimal uterine serous carcinoma: a clinicopathological study of 40 cases. *Mod Pathol* 2005;**18**:75–82.
15. Choo YC, Mak KC, Hsu C, Wong TS, Ma HK. Postmenopausal uterine bleeding of nonorganic cause. *Obstet Gynecol* 1985;**66**:225–8.
16. Iatrakis G, Diakakis I, Kourounis G *et al.* Postmenopausal uterine bleeding. *Clin Exp Obstet Gynecol* 1997;**24**:157.
17. Pritchard KI. Screening for endometrial cancer: is it effective? *Ann Intern Med* 1989;**110**:177–9.
18. Mitchell H, Giles G, Medley G. Accuracy and survival benefit of cytological prediction of endometrial carcinoma on routine cervical smears. *Int J Gynecol Pathol* 1993;**12**:34–40.
19. Broso PR, Giradi F. Is it possible to screen for endometrial carcinoma? Incidence and risk factors *Minerva Gynecol* 1995;**47**:539–52.
20. Kim YB, Ghosh K, Ainbinder S, Berek JS. Diagnostic and therapeutic advances in gynecologic oncology: screening for gynecologic cancer. *Cancer Treat Res* 1998;**95**:253–76.
21. Garcia F, Barker B, Davis J *et al.* Thin-layer cytology and histopathology in the evaluation of abnormal uterine bleeding. *J Reprod Med* 2003;**48**:882–8.
22. Buccoliero AM, Caldarella A, Noci I *et al.* Thin layer method in endometrial cytology. *Pathologica* 2003;**95**:179–84.

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23. Papaefthimiou M, Symiakaki H, Mentzelopoulou P *et al.* Study on the morphology and reproducibility of the diagnosis of endometrial lesions utilizing liquid-based cytology. *Cancer Cytopathol* 2005;**105**:56–64.
24. Taddei GL, Buccoliero AM. Atlante di citologia endometriale. *L'*endometrio normale, iperplastico e neoplastico nella citologia in fase liquida. Florence, Italy: SEE Editrice; 2005.
25. De Muylder X, Neven P, De Somer M, Van Belle Y, Vanderick G, De Muylder E. Endometrial lesions in patients undergoing tamoxifen therapy. *Int J Gynaecol Obstet* 1991;**36**:127–30.
26. Magriples U, Naftolin F, Schwartz PE, Carcangiu ML. High-grade endometrial carcinoma in tamoxifen-treated breast cancer patients. *J Clin Oncol* 1993;**11**:485–90.
27. Assikis VJ, Neven P, Jordan VC, Vergote I. A realistic clinical perspective of tamoxifen and endometrial carcinogenesis. *Eur J Cancer* 1996;**32A**:1464–76.
28. Koss LG, Schreiber K, Oberlander SG, Moukhtar M, Levine HS, Moussouris HF. Screening of asymptomatic women for endometrial cancer. *Obstet Gynecol* 1981;**57**:681–91.
29. Archer DF, McIntyre-Seltman K, Wilborn WW *et al.* Endometrial morphology in asymptomatic postmenopausal women. *Am J Obstet Gynecol* 1991;**165**:317–22.
30. Korhonen MO, Symons JP, Hyde BM, Rowan JP, Wilborn WH. Histologic classification and pathologic findings for endometrial biopsy specimens obtained from 2964 perimenopausal ad postmenopausal women undergoing screening for continuous hormones as replacement therapy (CHART 2 Study). *Am J Obstet Gynecol* 1997;**176**:77–380.
31. Nagase E, Yasuda M, Kajiwara H *et al.* Uterine body cancer mass screening at Tokai University Hospital. *Tokai J Exp Clin Med* 2004;**29**:43–8.
32. Grönroos M, Salmi TA, Vuento MH *et al.* Mass screening for endometrial cancer directed in risk groups of patients with diabetes and patients with hypertension. *Cancer* 1993;**71**:1279–82.
33. De Angelis C, Santoro G, Re ME, Nofroni I. Office hysteroscopy and compliance: mini-hysteroscopy versus traditional hysteroscopy in a randomized trial. *Hum Reprod* 2003;**18**:2441–5.
34. Agostini A, Bretelle F, Cravello L, Maisonneuve AS, Roger V, Blanc B. Acceptance of outpatient flexible hysteroscopy by premenopausal and postmenopausal women. *J Reprod Med* 2003;**48**:441–3.
35. Elsandabesee D, Greenwood P. The performance of Pipelle endometrial sampling in a dedicated postmenopausal bleeding clinic. *J Obstet Gynaecol* 2005;**25**:32–4.
36. Bakour SH, Khan KS, Gupta JK. Controlled analysis of factors associated with insufficient sample on outpatient endometrial biopsy. *Br J Obstet Gynaecol* 2000;**107**:1312–4.
37. Quinn M. Screening the high risk patient for gynaecological cancer. *Yonsei Med J* 2002;**43**:717–21.
38. Gupta JK, Chien PF, Voit D, Clark TJ, Khan KS. Ultrasonographic endometrial thickness for diagnosing endometrial pathology in women with postmenopausal bleeding: a meta-analysis. *Acta Obstet Gynecol Scand* 2002;**81**:799–816.
39. Rascoe RR. Endometrial aspiration smear in diagnosis of malignancy of the uterine corpus. *Am J Obstet Gynecol* 1963;**87**:921–5.
40. An-Foraker SH, Kawada CY, McKinney D. Endometrial aspiration studies on Isaacs cell sampler with cytohistologic correlation. *Acta Cytol* 1979;**23**:303–8.
41. Buratti E, Cefis F, Masserini M, Goisis F, Vergadoro F, Bolis G. The value of endometrial cytology in a high risk population. *Tumori* 1985;**28**:71.
42. Byrne AJ. Endocyte endometrial smears in the cytodiagnosis of endometrial carcinoma. *Acta Cytol* 1990;**34**:373–81.
43. LaPolla JP, Nicosia S, McCurdy C *et al.* Experience with the EndoPap device for the cytologic detection of uterine cancer and its precursors: a comparison of the EndoPap with fractional curettage or hysterectomy. *Am J Obstet Gynecol* 1990;**163**:1055–60.
44. Hecht EL. The endometrial aspiration smear; research status and clinical value. *Am J Obstet Gynecol* 1956;**71**:819–33.
45. Caubel P, Blondon J, Foulques H, Lefranc JP. Cancer of the endometrium: epidemiology, histology, diagnostic methods. *Rev Prat* 1990;**40**:31–5.
46. Stovall TG, Ling FW, Morgan PL. A prospective, randomized comparison of the pipelle endometrial sampling device with the Novak curette. *Am J Obstet Gynecol* 1991;**165**:1287–9.
47. Minagawa Y, Sato S, Ito M, Onohara Y, Nakamoto S, Kigawa J. Transvaginal ultrasonography and endometrial cytology as a diagnostic schema for endometrial cancer. *Gynecol Obstet Invest* 2005;**59**:149–54.