Cytological analysis of the distension fluid used during diagnostic office hysteroscopies in patients with suspected endometrial pathology

D. Gerbaldo[1], *M.D.*; A. Papadia[1], *M.D.*; P. Cristoforoni[1], *M.D.*; P. Lorenzi[3], *M.D.*; E. Fulcheri[2], *M.D.*; N. Ragni[1], *M.D.*

[1]Department of Obstetrics and Gynecology, [2]Department of Pathology, University of Genova
[3]Department of Obstetrics and Gynecology, Hospital of Imperia (Italy)

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Objective: Evaluation of the feasibility and usefulness of cytological analysis of the distension fluid used during diagnostic office hysteroscopy in patients with suspected endometrial pathology.

Methods: In 243 consecutive patients undergoing diagnostic hysteroscopy for suspected endometrial pathology a few milliliters of the distension medium used for uterine visualization were collected and sent for cytological analysis. Findings of these "endometrial washings" were compared to visual hysteroscopic impression, endometrial biopsy and uterine histology – when available.

Results: Endometrial washings were considered adequate in 227 patients (93.4%). In 12 cases (5.3%) atypical cells were detected: all of these presented either atypical complex hyperplasia or endometrial cancer at the final histological evaluation of the uterus. Four of the 16 (25%) patients diagnosed with endometrial cancer or atypical complex hyperplasia at the final histopathological analysis of the uterus had inadequate washings. No patient with cancer or atypical hyperplasia had negative cytology.

Conclusions: Collection and analysis of the distension fluid is feasible and, when positive, has a remarkable value in the diagnosis of endometrial cancer and its precursors.

Key words: Endometrial cancer; Atypical hyperplasia; Cytology; Hysteroscopy.

Introduction

Endometrial cancer is the most common cancer of the genital tract in Western countries with an incidence of 15-20/100,000 women per year [1]. Since the first sign of endometrial cancer is usually abnormal uterine bleeding, the management of women presenting with this sign is an important issue [2].

Many of these patients will undergo hysteroscopy as part of their diagnostic flowchart. Hysteroscopy has a very high accuracy when compared to the histological findings at hysterectomy in detecting endometrial cancer [3, 4]. However the accuracy in detecting hyperplasia is much lower [4, 5]. Furthermore it is believed that a pathological alteration is not necessarily morphologically evident, in that cytological atypia is the only important morphologic feature that identifies endometrial lesions with invasive potential [6-8].

Adding to each hysteroscopy a representative sampling of the entire endometrial cavity could therefore be clinically useful. Theoretically, when performing hysteroscopies, endometrial cells should exfoliate from the entire endometrial lining because of the stretch of the cavity and because of the turbulence created by the liquid used as distension medium and collected in the liquid itself. If this is proved to be true, and if the cytological features of these cells can be evaluated by a pathologist, the recovery of the distension medium may provide a cytological sampling representative of the entire endometrial lining.

We have tried to investigate if the retrieved distension medium used for performing hysteroscopies contained endometrial cells, if it was possible to analyze their features and if their pathological analysis would add any useful information in the decision-making process.

Histological and cytological samplings ("endometrial washings") were performed on women presenting with abnormal uterine bleeding and/or a suspect endometrial echo pattern undergoing office-hysteroscopy. Feasibility of the "endometrial washing", sensitivity and specificity, PPV and NPV of both sampling methods and of hysteroscopy were evaluated and compared.

Materials and Methods

From September 2000 to March 2003 we performed 243 outpatient office hysteroscopies with eye-guided endometrial biopsies on women with abnormal uterine bleeding and/or ultrasonographic suspicion of endometrial pathology. The vaginoscopic approach and saline solution as uterine distension medium were used as described elsewhere [9]. Hysteroscopy was performed using Karl Storz 4.5 mm scopes and 3 CCD cameras. Room temperature 0.9% saline solution suspended about 90 cm over the patient level was used as distension medium. Local anesthesia or drug premedication was not performed.

After having achieved complete visualization of the endometrial cavity the infusion of distension medium was stopped and the liquid contained in the cavity was retrieved by opening the

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operative channel of the hysteroscope and collected in a test tube, which was sent to the pathologist without further preparation. Each sample had a volume of about 7 ml.

The pathologist (E.F.) blindly viewed all cytological and histological specimens.

"Endometrial washings" and biopsies were considered inadequate when the samples lacked cellularity; hysteroscopy was considered inadequate when the entire uterine cavity could not be properly visualized.

The results of the cytological samplings were called positive in the presence of atypical endometrial cells and negative if cellular atypias were lacking.

Criteria for defining atypical cells are described elsewhere [10-13].

In each case an eye-guided biopsy was performed at the end of the procedure. The biopsy was performed on the most suspicious finding or, if there were no suspicious findings, on the most representative region of the endometrium.

Histology was called positive when atypical hyperplasia or cancer was diagnosed. Hysteroscopy was called positive when a high-risk polyp or a lesion morphologically suggestive of high-risk hyperplasia or endometrial cancer was seen.

All patients with findings suggestive of atypia or endometrial cancer (either at endometrial washing, biopsy or hysteroscopy) were suggested to undergo a surgical procedure: D&C was performed in two cases (with a positive hysteroscopy and negative endometrial biopsy and washing), while 16 patients directly underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO) and, if indicated, pelvic lymphadenectomy.

Written informed consent was obtained from every patient.

The cytological and histological diagnosis and the hysteroscopic description were compared with the final histopathological diagnosis of the D&C or of the uterus. Feasibility of the "endometrial washing", sensitivity and specificity, PPV and NPV for endometrial washing, endometrial biopsy and hysteroscopy were calculated.

Results

Mean age of the patients was 53 years (range 23-95); 170 women were in postmenopause and 73 women were still menstruating.

An "endometrial washing" could be obtained from every patient. In 16 patients (6.5%) the liquid lacked cellularity and was considered inadequate by the pathologist. In the remaining 227 patients (93.5%) the sample contained cells with cytological features that could be analyzed (Table 1).

The results of the cytological analysis of the "endometrial washings" were subsequently compared with those of the hysteroscopy and endometrial biopsy.

The results of the procedures (cytology, histology, hysteroscopy) are summarized in Table 1.

Table 1. — *Cytological, histological and hysteroscopic findings.*

	EMW (No. of pts)	EMB (No. of pts)	HS (No. of pts)
Not adequate	16 (6.6%)	17 (7.0%)	9 (3.7%)
Positive	12 (4.9%)	13 (5.3%)	14 (5.8%)
Negative	215 (88.5%)	213 (87.6%)	220 (90.5%)

EMW: Endometrial washing. EMB: Endometrial biopsy. HS: Hysteroscopy.

Negative findings are summarized in Table 2. One patient had inadequate hysteroscopy, biopsy and "endometrial washing".

In 18 cases there was at least one positive finding: atypical cells at "endometrial washing", atypical hyperplasia or endometrial cancer at biopsy, high-risk polyp, high-risk hyperplasia or endometrial cancer at hysteroscopy (Table 3). Two of these patients underwent D&C while the remaining 16 patients underwent TAH-BSO.

In the two patients who underwent D&C final histopathological analysis revealed simple and complex endometrial hyperplasia without atypia: in these cases D&C was suggested by a positive hysteroscopy while both endometrial biopsy and "endometrial washing" were negative. These patients underwent another hysteroscopy one month later, which confirmed the negative results of endometrial biopsy, washing and D&C.

In the other 16 cases final analysis of the uterus revealed endometrial cancer in 14 and endometrial atypical complex hyperplasia in two cases. Hysteroscopy was negative or inadequate in four cases; endometrial biopsy was negative in three and "endometrial washing" was inadequate in four cases. No patient with a final diagnosis of endometrial cancer or atypical hyperplasia presented adequate negative "endometrial washing".

Of the nine cases with inadequate hysteroscopy seven turned out to be negative and two positive, of the 16 cases with inadequate "endometrial washings" 12 were negative and four positive, while 17 cases with inadequate endometrial biopsy were all negative.

In one patient (0.4%) all the procedures (hysteroscopy, endometrial biopsy and "endometrial washing") were considered inadequate; this patient underwent D&C and histopathologic analysis was consistent with endometrial atrophy. Hysteroscopy was repeated 30 days later and resulted negative for endometrial pathology.

Table 2. — *Patients without positive findings at hysteroscopy, endometrial biopsy and/or endometrial washing.*

No. of patients	Hysteroscopy	Endometrial washing	Endometrial biopsy
193 (79.4%)	Negative	Negative	Negative
6 (2.5%)	Not adequate	Negative	Negative
2 (0.8%)	Negative	Not adequate	Not adequate
9 (3.7%)	Negative	Not adequate	Negative
14 (5.8 %)	Negative	Negative	Not adequate
1 (0.4 %)	Not adequate	Not adequate	Not adequate

Table 3. — *Patients with positive findings at hysteroscopy, endometrial washing and/or endometrial biopsy.*

No. of patients (%)	Hysteroscopy	Endometrial washing	Endometrial biopsy	Hysterectomy
7 (2.9%)	+	+	+	+
2 (0.8%)	-	+	-	+
1 (0.4%)	+	+	-	+
2 (0.8%)	NA	+	+	+
4 (1.6%)	+	NA	+	+
2 (0.8%)	+	-	-	- (*)

Total number of patients with at least one positive finding: 18.
+: Positive. -: Negative. NA: Not adequate. (*): D&C.

An "endometrial washing" could be collected in 100% but lacked cellularity in 6.5% of the cases. When the sample was considered adequate (93.4% of the cases) the definition of the cytological features was always possible and sensitivity, specificity, PPV and NPV were 100%. Overall sensitivity and specificity for hysteroscopy and for endometrial biopsy were 85.7% and 99.1% and 81.2% and 100%, respectively. PPV and NPV were respectively 85.7% and 99.1% for hysteroscopy and 100% and 94.2% for endometrial biopsy (Table 4).

Table 4. — *Sensitivity, specificity, PPV and NPV of the procedures in detecting endometrial cancer or atypical hyperplasia.*

	Sensitivity	Specificity	PPV	NPV
Endometrial washing (EMW)	100% (CI: 73.5-100)	100% (CI: 98.3-100)	100%	100%
Endometrial biopsy (EMB)	81.2% (CI: 54.4-96.0)	100% (CI: 98.3-100)	100%	94.2%
Hysteroscopy (HS)	85.7% (CI: 57.2-98.2)	99.1% (CI: 96.8-99.9)	85.7%	99.1%

CI: 95% confidence.

Discussion

During the last decade hysteroscopy has been widely used in the assessment of abnormal uterine bleeding [14, 15].

Hysteroscopy has been shown to have a very high accuracy, with a reported sensitivity and specificity of 98% and 95%, respectively [3]. However this is not a perfect technique. It is more accurate and clinically useful in diagnosing endometrial cancer than in excluding it in women with abnormal uterine bleeding; its accuracy in predicting endometrial hyperplasia is however much lower [4, 5].

Even by combining hysteroscopy with an endometrial biopsy misdiagnoses can occur [16-18].

They can be explained either by the fact that target biopsies performed with an operative hysteroscope might be too small to be correctly analyzed by the pathologist or that the biopsies could have been done in the wrong site.

Moreover, a morphologic evident lesion might not be associated with an important pathologic alteration, whereas the latter may arise without clear evidence of macroscopic alterations. It is believed that the important feature distinguishing endometrial hyperplasia from neoplasia is cytological atypia, and it is no longer widely accepted that hyperplastic lesions form a continuum of morphologic severity. Cytological atypia is probably the only important morphologic feature that identifies endometrial lesions with invasive potential [6-8].

If what is stated above is true, a sampling of the entire uterine cavity after each hysteroscopy could help to rule out lesions that are not morphologically evident. Theoretically, the best sampling technique of the uterine cavity would be one which allows a cytological analysis of endometrial cells which are representative of the entire endometrial lining.

During hysteroscopy, the saline solution used for distending the uterine cavity and the distension of the cavity itself are probably responsible for the exfoliation of endometrial cells from the endometrial lining.

After having exfoliated from the epithelium, endometrial cells float in the distension medium and can be collected and their features analyzed by retrieving the distension fluid.

"Endometrial washing" was clinically useful in at least two cases. In our series the presence of atypical cells in the "endometrial washing" was the only finding suggesting a malignancy or a high-risk precursor of a malignancy of the endometrium in two patients; final histopathological analysis of the uterus revealed endometrial cancer in one case and atypical complex hyperplasia in the other.

When "endometrial washing" is adequate (93.4% of the cases) it has a sensitivity, specificity, PPV and NPV of 100%. These results are better than those obtained by hysteroscopy and endometrial biopsy. In our hands sensitivity, specificity, PPV and NPV of hysteroscopy were comparable with those reported in the literature [3, 19].

This technique combines the advantages offered by hysteroscopy (direct visualization of the endometrium and possibility to perform an eye-guided biopsy) with those of a sampling of the entire cavity.

Even though we did not perform a cost analysis of this new sampling technique, it appears to be convenient. First of all because the cytological analysis is performed on "recycled" fluid which collects endometrial cells while distending the uterine cavity, and secondarily because of the reduced pathology charges for cytology.

In our preliminary results the performance of "endometrial washing" at the time of hysteroscopy and its cytological examination appeared to be feasible, representative of the entire cavity and clinically useful. Further studies performed with a larger number of patients should be carried out to confirm the validity of this technique.

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Address reprint requests to:
A. PAPADIA, M.D.
Dipartimento di Ginecologia e Ostetricia
Università di Genova
Ospedale "San Martino"
Largo R. Benzi Pad 1
16132 Genova (Italy)