# Endometrial study in patients with postmenopausal metrorrhagia

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## Abstract

**Introduction:** The aim of the study was to devise a strategy to diagnose malign endometrial pathologies (adenocarcinoma or atypical hyperplasia) that minimizes the number of invasive tests done (hysteroscopy, aspiration biopsy or curettage) with no loss of its detection efficiency.

**Material and methods:** We retrospectively studied the clinical histories of 779 postmenopausal women at the University Hospital Complex of Albacete, for whom an endometrial study had been done (hysteroscopy, aspiration biopsy or curettage) with a 1-year follow-up between 1 March 2006 and 31 March 2008.

**Results:** There were 77 cases of a malignant pathology (66 adenocarcinomas and 11 hyperplasias with atypia); 96.1% had metrorrhagia, and there were only 3 cases of asymptomatic patients (all 3 presented endometrial thickness of > 5 mm: 10, 12 and 15 mm). The sensitivity and specificity of the transvaginal ultrasound, with a 5 mm cut-off point to diagnose a malignant pathology, were 98.4% and 30.1%, respectively; 89.1% and 99.6%, respectively, for aspiration biopsy; 83.9% and 99.1%, respectively, for hysteroscopy without biopsy; and both were 100% for biopsy. Statistical significance was considered at $p < 0.05$ and confidence intervals were calculated at 95%.

**Conclusions:** In postmenopausal women with metrorrhagia, the first action to take is to do a transvaginal ultrasound, followed by en endometrial study, but only if the endometrium is irregular or endometrial thickness is ≥ 5 mm; in asymptomatic women, the cut-off point should be set at 10 mm. The immediate method of choice is an ambulatory biopsy.

**Key words:** adenocarcinoma, aspiration biopsy, metrorrhagia, hysteroscopy, ultrasound.

## Introduction

Endometrial adenocarcinoma is the most frequent feminine tumor of the lower genital tract in developed countries. It is 40% more frequent than ovarian cancer, more than double the number of cervical cancer cases, and it has the highest frequency after breast, colon and lung cancer [1]. Abnormal uterine bleeding is the presenting symptom in 75–90% of cases. The majority of patients with endometrial cancer are diagnosed with no evidence of extrauterine spread (70–80% stage I), which gives

patients a better prognosis. In more advanced disease the sites commonly affected outside the uterus are pelvic and para-aortic lymph nodes and the ovaries. Although not usual, it has also been described in bone metastases [2]. Given its frequency, we decided to look for a strategy to diagnose it by minimizing the invasive tests done on the endometrium, but without loss of reliability of diagnoses of the malign endometrial pathology, by considering both adenocarcinoma and hyperplasia with atypia.

A transvaginal ultrasound is a less invasive test and proves quite useful when having to discriminate cancer or hyperplasia depending on endometrial thickness in a postmenopausal patient [3]. It is a valid preliminary test in patients with metrorrhagia, and those who obtain a positive result in it (endometrial thickness values of 4–5 mm, according to some authors [4]) should undergo more invasive studies, such as a hysteroscopy or an endometrial biopsy [4, 5]. Finally, a diagnostic curettage [6] should be employed only for special cases in which the performance of the previous tests is not feasible.

## Material and methods

### Patients studied

We carried out a descriptive, cross-sectional retrospective study of 779 postmenopausal patients who were submitted to an endometrial study, defined by performing diagnostic hysteroscopy and/or histological study, with a 1-year follow-up in the University Hospital Complex of Albacete between 1 March 2006 and 31 March 2008.

### Procedures

We have created two large diagnostic group:

1) Malign pathology: includes cases of adenocarcinoma or hyperplasia with atypia.
2) Malign and precursor pathology: includes group 1 (cases of adenocarcinoma or hyperplasia with atypia) and hyperplasia without atypia.

An ambulatory biopsy is done during the consultation, which requires no preparation by the patient, by introducing a Cornier cannula through the cervix to obtain a sample by aspiration.

A diagnostic curettage is performed surgically with general anesthetic after hospitalizing the patient.

An ambulatory diagnostic hysteroscopy is carried out in the hospital's Diagnostic Hysteroscopy Unit using oral analgesia and diazepam. Depending on the findings, an assisted biopsy is carried out, or not. On occasion, a blind biopsy is done with a Cornier or a Novak cannula to finish the technique if we consider that an assisted biopsy does not suffice.

### Data collection

To carry out this study, two databases were used: the diagnostic hysteroscopy database and the anatomic pathologic database. After considering the inclusion criteria (being postmenopausal and having undergone all the supplementary tests in our center) and the exclusion criteria (not having access to clinical histories and not having a definite diagnosis) with all the patients, 595 diagnostic hysteroscopies with or without assisted biopsy and 322 endometrial biopsies (305 aspiration biopsies and 17 curettages) were carried out. Some patients had more than one test done. In all, 779 patients were studied.

After completing patient selection, we collected the data of the procedures done (aspiration biopsy, diagnostic hysteroscopy and curettage) and the diagnosis received. After for a year, we related it to the retrospective clinical data (collected from their clinical histories) to find a connection, as these data were those that motivated us to do this study.

### Statistical analysis

The association between the qualitative variables was assessed using a Pearson $\chi^2$ test by calculating the odds ratios (ORs) with their 95% confidence intervals (CI). To adjust risks for possible confounding variables, we did a multivariate analysis by non-conditional logistic regression. When calculating the sensitivity and specificity of the tests employed, the following cut-off points were considered for their positivity: transvaginal ultrasound, for which we set the cut-off point for endometrial thickness measured longitudinally as being greater than or equal to 5 mm; ambulatory biopsy, for which we set two cut-off points: firstly, we considered the adenocarcinoma or hyperplasia with atypia results to be a positive biopsy; secondly, we considered the adenocarcinoma or hyperplasia with and without atypia results to be a positive biopsy; diagnostic hysteroscopy, for which we set two cut-off points: firstly, we evaluated the diagnostic capacity of a hysteroscopy to diagnose a malign pathology by considering an image suggestive of adenocarcinoma to be positive; secondly, we evaluated the diagnostic capacity of a hysteroscopy to diagnose a malign pathology by considering an image suggestive of adenocarcinoma or hyperplasia to be positive.

For the ratios, 95% confidence intervals were calculated by the Fisher method with the OpenEpi program. Statistical significance was considered to be $p < 0.05$, and all the confidence intervals were calculated at 95%.

## Results

The diagnoses made after performing the study are presented in Table I.

## Transvaginal ultrasound

The sensitivity of the transvaginal ultrasound for adenocarcinoma by using a endometrial thickness cut-off point of 5 mm was 98.4%, and its specificity was 30%. For malign pathology (adenocarcinoma or hyperplasia with atypia), these values rose slightly to 98.7% and 30.1%, respectively. Finally for malign or precursor pathology, the values obtained were 95% and 32.2%, respectively.

Table II describes the ratio of the transvaginal ultrasound findings depending on the pathology diagnosed.

Further transvaginal ultrasound information to be considered is the presence of intracavity fluid, as of the 16 patients who presented it, 8 (50%) were diagnosed as having adenocarcinoma.

We selected the cases of patients who presented metrorrhagia, which we related to the scan findings and the definite diagnoses at the end of the study. We found no case of malignant pathology among the patients with a regular atrophic endometrium (95% CI: 0–2.6), and there was only 1 adenocarcinoma case among the 33 patients with an irregular atrophic endometrium (3%; 95% CI: 0.07–15.7).

Among the asymptomatic patients, only 3 cases of malignant pathology were found, with a hypertrophic endometrium in them all (2 adenocarcinomas with endometrial thickness (ET) of 12 mm and 15 mm, and 1 hyperplasia with atypia and ET of 10 mm).

**Table I.** Definite diagnosis of the 779 studied patients

| Definite diagnosis | Number | Percentage |
|---|---|---|
| Normal† | 331 | 42.5 |
| Benign pathology# | 306 | 39.3 |
| Hyperplasia without atypia | 65 | 8.3 |
| Hyperplasia with atypia | 11 | 1.4 |
| Adenocarcinoma | 66 | 8.5 |

†*Atrophic endometrium, weakly proliferative endometrium, secondary endometrial changes to treatment, septate uterus or endometrial adherences.* #*Polyp or myoma.*

## Aspiration biopsy

The results of the 305 aspiration biopsies performed are presented in Table III. To study the diagnostic capacity of an aspiration biopsy, we set two cut-off points for the biopsy result to be considered positive: cut-off point 1 was the adenocarcinoma or hyperplasia with atypia results considered to be a positive biopsy. Using this cut-off point to diagnose a malignant pathology, the sensitivity and specificity values of the aspiration

**Table II.** Proportion of all the transvaginal ultrasound findings according to the pathology diagnosed

| Transvaginal ultrasound finding† | AC (*n* = 66) | HWA (*n* = 11) | HNA (*n* = 63) | BP (*n* = 295) | Normal (*n* = 312) |
|---|---|---|---|---|---|
| E. Regular atrophy | 0 | 0 | 0 | 13 | 136 |
| E. Irregular atrophy | 1 | 0 | 6 | 25 | 22 |
| E. Regular hypertrophy | 9 | 4 | 19 | 67 | 102 |
| E. Irregular hypertrophy | 56 | 7 | 38 | 190 | 52 |

†*We have 747 transvaginal ultrasound findings of all the 779 patients included in this study. AC – adenocarcinoma, HWA – hyperplasia with atypia, HNA – hyperplasia with no atypia, BP – benign pathology (polyp or myoma), Normal – weakly proliferative atrophic endometrium with secondary changes to treatment, adherences or septate uterus.*

**Table III.** Relation between the results of the aspiration biopsy and the definite diagnosis

| AB results | Definite diagnosis at the end of the study | | | | | |
|---|---|---|---|---|---|---|
| | Normal | BP | HNA | HWA | AC | Total |
| IS | 49 | 20 | 5 | 0 | 2 | 76 |
| Normal | 135 | 28 | 6 | 1 | 0 | 170 |
| BP | 0 | 7 | 3 | 1 | 0 | 11 |
| HNA | 0 | 1 | 4 | 0 | 1 | 6 |
| HWA | 1 | 0 | 0 | 0 | 1 | 2 |
| AC | 0 | 0 | 0 | 0 | 40 | 40 |
| Total | 185 | 56 | 18 | 2 | 44 | 305 |

*AB – aspiration biopsy, Normal – weakly proliferative atrophic endometrium or with secondary changes to treatment, BP – benign pathology (polyp or myoma), HNA – hyperplasia with no atypia, HWA – hyperplasia with atypia, AC – adenocarcinoma, IS – insufficient sample.*

biopsy were 89.1% (95% CI: 76.96–95.27) and 99.6% (95% CI: 97.85–99.93), respectively, with a positive predictive value of 97.6% (95% CI: 87.6–99.58) and a negative predictive value of 98.1% (95% CI: 95.63–99.19).

The biopsy diagnosed the only case of adenocarcinoma in a patient who presented an irregular atrophic endometrium in the scan and metrorrhagia. Cut-off point 2 was the adenocarcinoma and hyperplasia (with and without atypia) results considered to be a positive biopsy. Using this cut-off point to diagnose a malignant or precursor pathology, the sensitivity and specificity values of the aspiration biopsy were 71.8% (95% CI: 59.87–81.45) and 99.1% (95% CI: 97.03–99.77), respectively, with a positive predictive value of 95.83% (95% CI: 86.02–98.85) and a negative predictive value of 93% (95% CI: 89.2–95.52).

### Hysteroscopy

We performed 595 hysteroscopies, and the obtained results are provided in Table IV. To study the diagnostic capacity of the hysteroscopy, we set two cut-off points where the hysteroscopy result is considered positive: cut-off point 1: we evaluated the diagnostic capacity of the hysteroscopy to diagnose a malignant pathology by considering an image suggestive of adenocarcinoma to be positive. The sensitivity and specificity of the hysteroscopy without assisted biopsy to diagnose a malignant pathology were 64.3% (95% CI: 48.0–78.4%) and 99.3% (95% CI: 98.2–99.8) respectively, with a positive predictive value of 87% (95% CI: 70.1–96.3) and a negative predictive value of 97.3% (95% CI: 95.3 and 98.5). Cut-off point 2: we evaluated the diagnostic capacity of the hysteroscopy to diagnose a malignant pathology by considering an image suggestive of adenocarcinoma or hyperplasia to be positive. The sensitivity and specificity of the hysteroscopy without assisted biopsy to diagnose a malignant pathology were 92.8% (95% CI: 80.5–98.5%) and 73.6% (95% CI: 69.9–77.1%), respectively, with a positive predictive value of 24.8% (95% CI: 18.3–32.3) and a negative predictive value of 99.3% (95% CI: 98.1–99.8).

### Diagnostic curettage

We carried out this procedure in 17 patients, of whom 7 had adenocarcinoma and were correctly diagnosed by curettage. The results have a limitation due to the small sample size.

## Discussion

Most of the patients diagnosed with a malignant pathology included in our study had come to consultations for metrorrhagia. The first step was to do a transvaginal ultrasound, where we observed, except for 1 patient with an irregular atrophic endometrium, that the remaining patients with a malignant pathology presented hypertrophic endometrium. The high aspiration biopsy sensitivity obtained to diagnose a malignant pathology allowed us to employ this diagnostic test as a first study step after performing the transvaginal ultrasound. In those cases in which the diagnosis was doubtful, diagnostic hysteroscopy with an assisted biopsy provided 100% sensitivity when detecting a malignant pathology.

The strong point of this study lies in the large number of patients studied and the homogeneous vision of the hysteroscopy specialists and pathologists, as the same specialists always performed the same techniques.

The study limitations are mainly due to its retrospective nature which made data organization a difficult task because some data were not available for all the patients. Furthermore, when analyzing the diagnostic techniques performed, the sample was not homogeneous because there were many more patients who had undergone a diagnostic hysteroscopy than those who had been referred for an ambulatory biopsy or curettage.

**Table IV.** Relation of the hysteroscopy findings and the definite diagnosis

| HSC results | Definite diagnosis at the end of the study | | | | | |
|---|---|---|---|---|---|---|
| | Normal | BP | HNA | HWA | AC | Total |
| Normal | 182 | 1 | 0 | 0 | 0 | 183 |
| Benign-looking polyp | 0 | 221 | 17 | 3 | 0 | 241 |
| Myoma | 0 | 14 | 0 | 0 | 0 | 14 |
| Hyperplastic E. or P. | 7 | 65 | 42 | 7 | 5 | 126 |
| AC | 0 | 1 | 3 | 1 | 26 | 31 |
| Total | 189 | 302 | 62 | 11 | 31 | 595 |

*HSC – hysteroscopy, Normal – weakly proliferative atrophic endometrium or with secondary changes to treatment, BP – benign pathology (polyp or myoma), HNA – hyperplasia with no atypia, HWA – hyperplasia with atypia, AC – adenocarcinoma, E – endometrium, P – polyp.*

### Transvaginal ultrasound

This technique is a less invasive test and proves quite useful when having to discriminate cancer or hyperplasia depending on endometrial thickness in a postmenopausal patient, and it is valid as an initial test in patients with metrorrhagia [7]. If its result is positive (ET values between 4 mm and 5 mm, according to some authors) [4, 8, 9], performing a hysteroscopy is recommended [10, 11].

The meta-analysis of Smith-Bindman *et al.* [12] with postmenopausal women reported that 96% of women with a malignant endometrial pathology and 92% of those with some endometrial disorder presented an ET over 5 mm and that the specificity for endometrial cancer with this cut-off point was 68%. Our results coincide with these data.

In the asymptomatic patients, several studies indicate that a transvaginal ultrasound is not a good screening method [13–15]. A good cut-off point to conduct further studies in postmenopausal patients would be 10 mm based on our results and as compared with those reported by other authors [16].

### Aspiration biopsy

The clinical guidelines of the Royal College of Obstetricians and Gynaecologists (RCOG) [17] contemplates that endometrial biopsy sensitivity in postmenopausal women who do not present an endometrial pathology is lower, probably due to endometrial atrophy, as we verified in our results: for 26.4% of the women presenting atrophic endometria, the sample collected by an ambulatory biopsy proved insufficient to make a diagnosis. If cancer had been present, this probability of failure to obtain a sample would be markedly lower. The false-negative rate for endometrial cancer for these patients was very low and could, therefore, be excluded (sensitivity and specificity of 99.6% and 91.0%, respectively [18]). In general, further cavity evaluation should be made if symptoms persist or recur, or if structural endometrial anomalies are suspected [17].

The false negatives in our study were basically due to lesions on polyps. Despite the endometrial biopsy being a useful and inexpensive test to identify endometrial malignancy and premalignancy, it is a poor test to diagnose endometrial structural anomalies such as submucous polyps and myoma [18].

Thus, we consider that the ambulatory biopsy offers high sensitivity in homogeneous hypertrophic endometria, but lower sensitivity in non-homogeneous cases. Our recommendation, which coincides with that made by other authors [19], is to immediately perform an aspiration biopsy with patients with postmenopausal metrorrhagia and hypertrophic endometria (irrespectively of them being homogeneous or not), and also in postmenopausal patients who do not present metrorrhagia, but an endometria of ≥ 10 mm, because it is a simpler, less awkward technique with fewer complications than a diagnostic hysteroscopy. We would resort to a hysteroscopy only if the result was not a malignant pathology, and despite our suspicions, in order to continue the study.

### Hysteroscopy

The range of overall hysteroscopy sensibility is 92–97%, and the false negatives obtained are at the expense of an endometrial hyperplasia [20], as in our study, and an assisted endometrial biopsy is always indicated whenever in doubt. Other authors offer studies with a sensitivity and specificity value of the hysteroscopy image to predict endometrial cancer of 50.0% and 99.5%, respectively, and they state that a hysteroscopy must always accompany an endometrial biopsy because an image alone is not sensitive enough to specify whether we are faced with a malign or benign process [21]. Bedner and Rzepka-Górska calculated the sensitivity of diagnosis in a hysteroscopic image of several lesions [22]. The agreement of the macroscopic image with the anatomo-pathological report was variable according to lesion type, with 90.9% in submucous myoma, 86.9% in endometrial polyps, 25.0% in endometrial hyperplasia and 71.4% in endometrial carcinoma cases. This author concluded that the hysteroscopic vision was not sufficient to diagnose a malignant or premalignant pathology. Hence taking an assisted biopsy would always be indicated, as we have verified with our results.

Hysteroscopy specificity for endometria with no pathology (atrophic, weakly proliferative or with secondary changes to treatment) was 99.7%, which is similar to that which has been reviewed [21]. The RCOG recommends performing biopsies even with a normal hysteroscopy [17]. Nowadays, it is recommended to combine a hysteroscopy with biopsies if a scan finds that the endometrium is over 4 mm, and to carry out curettage of the cavity if malignancy is suspected despite a normal hysteroscopy image [17].

In conclusion, the study of a postmenopausal patient with metrorrhagia must begin by doing a transvaginal ultrasound and performing other tests in accordance with the endometrial thickness found. We consider it correct to continue the study if faced with irregular endometria or endometrial thickness of ≥ 5 mm as a first option by an ambulatory biopsy, and by a diagnostic hysteroscopy if in doubt.

## Conflict of interest

The authors declare no conflict of interest.

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