Hysteroscopic findings in postmenopausal patients with ultrasonographic diagnosis of endometrial thickening

Achados histeroscópicos em pacientes na pós-menopausa com espessamento endometrial à ultra-sonografia

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ABSTRACT

Objective: To evaluate the results of hysteroscopy for investigating the uterine cavity of postmenopausal women presenting endometrial thickening on ultrasound. **Methods:** A cross-sectional study was conducted on hysteroscopic evaluations of 329 postmenopausal women presenting with endometrial thickening on transvaginal ultrasonography. Hysteroscopies were performed in an outpatient setting, using a 4 mm optic Hamou II microhysteroscope and gas (CO_2) to distend the uterine cavity. A guided biopsy for histology was performed in all patients with suspected endometrial malignancies and in most patients with benign abnormalities. **Results:** Endometrial thickness ranged from 6 to 38 mm (mean of 10.03 $\pm$ 4.49 mm). The hysteroscopic findings were polyps in 183 patients (55.62%); atrophic endometrium in 55 patients (16.72%); synechia in 26 patients (7.90%); a "cerebroid" appearance lesion in 13 patients (3.95%); myoma in 12 patients (3.65%); endometrial hyperplasia in 11 patients (3.34%); focal thickening in ten patients (3.04%); proliferative endometrium in eight patients (2.43%); mucus in seven patients (2.13%); and cystic atrophy in four patients (1.22%). Endometrial carcinoma was confirmed by histology in 11 of 13 suspected cases, in which hysteroscopy showed the cerebroid appearance. Hyperplasias were confirmed in seven of 11 cases. The respective accuracy was 99.26 and 96.67%. Nine out of 11 endometrial cancer cases and six out of 12 hyperplasia cases presented uterine bleeding. **Conclusions:** The most frequent findings were benign lesions (92.71%). Hysteroscopy with biopsy is an accurate method to detect intracavitary uterine disease.

Keywords: Endometrial hyperplasia/ultrasonography; Endometrium/pathology; Postmenopause; Hysteroscopy; Histology

RESUMO

Objetivo: Avaliar os resultados da histeroscopia na investigação da cavidade uterina de mulheres na pós-menopausa com espessamento endometrial à ultra-sonografia. **Métodos:** Realizou-se estudo transversal, com avaliação histeroscópica de 329 mulheres na pós-menopausa, com diagnóstico de espessamento endometrial à ultra-sonografia transvaginal. As histeroscopias foram realizadas em ambiente ambulatorial, utilizando-se um micro-histeroscópico de Hamou II, com óptica de 4 mm e meio gasoso (CO_2) para a distensão da cavidade uterina. A biópsia orientada foi efetuada em todas as pacientes com alterações suspeitas de malignidade e, na maioria das pacientes com alterações benignas o material obtido foi submetido a estudo histopatológico. **Resultados:** A espessura endometrial variou de 6 a 38 mm, com média de 10,03 $\pm$ 4,49 mm. Os achados histeroscópicos foram: pólipos em 183 pacientes (55,62%); endométrio atrófico em 55 (16,72%); sinéquia em 26 (7,9%); lesão com aspecto "cerebróide" em 13 (3,95%); mioma em 12 (3,65%); hiperplasias endometriais em 11 (3,34%); espessamento focal em dez (3,04%:); endométrio proliferativo em oito (2,43%); muco em sete (2,13%) e atrofia cística em quatro (1,22%). Houve confirmação histológica de câncer de endométrio em 11 dos 13 casos sugestivos à histeroscopia de aspecto "cerebróide". As hiperplasias foram confirmadas em sete dos 11 casos. A acurácia foi respectivamente

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de 99,26 e 96,67%. Nove dos 11 casos de câncer de endométrio e seis dos 12 casos de hiperplasias apresentavam sangramento uterino. **Conclusões:** Os achados histeroscópicos mais freqüentes encontrados foram de lesões benignas (92,71%). A histeroscopia com biópsia mostrou-se método de elevada acurácia na identificação de anormalidades intra-uterinas.

Descritores: Hiperplasia endometrial/ultra-sonografia; Endométrio/patologia; Endométrio/ultra-sonografia; Pós-menopausa; Histeroscopia; Histologia

INTRODUCTION

Cancer of the uterine body is the most common gynecological malignancy in the United States of America. As female life expectancy increases worldwide, especially in developed countries, the natural course of other gynecological tumors becomes altered by prevention and screening measures.

The importance and relevance of endometrial carcinoma is also increasing. In Brazil, endometrial adenocarcinoma is the second most common pelvic tumor; its incidence is of six to eight cases per 100,000 women. The mean age of diagnosis is about 60 years; 75% of patients are postmenopausal and less than 5% are aged below 40 years[1].

Endometrial epithelial gland cells proliferate due to the effect of estrogens, which may result in hyperplasic growth and eventually endometrial cancer. These proliferative effects are counterbalanced by the secretory effect of progesterone[2]. Atypical hyperplasia carries the highest risk of progressing to cancer. The risk of hyperplasia with no atypias progressing to carcinoma is 1% when simple, and 3% when complex. The corresponding risk for atypical hyperplasia is 8% when simple and 29% when complex[1].

Genital bleeding is the main clinical manifestation of endometrial carcinoma. Medically, however, most women are asymptomatic[3]. Thus, the importance of investigating the endometrium to detect precancerous lesions and the carcinoma itself increases. The main screening methods for the uterine cavity are: endometrial cytology, uterine curettage and hysteroscopy.

Hysteroscopy is the most appropriate method to assess the uterine cavity in women presenting endometrial thickening with or without symptoms. It is a dynamic exam that may be performed in an outpatient setting, and which allows a direct view of the endometrium. Its main advantage is that biopsies are possible, which improves the diagnostic accuracy, particularly of focal lesions[4].

Transvaginal ultrasound is essential to assess the causes of postmenopausal bleeding, the endometrium in asymptomatic patients, and any pelvic cavity alteration. However, ultrasound cannot differentiate between polyps, hyperplasia and proliferative phenomena due to hormone therapy[4]; it also cannot differentiate exactly the location of submucosal or intramural myomas[5]. Smith-Bindman et al.[6] showed that ultrasound is highly sensitive to detect endometrial abnormalities (92%) when using a 5-mm cutoff point; specificity, however, is low (61%). Costs and anxiety increase, when ultrasound suggests an abnormality and pathological exam, discards any endometrial disease.

OBJECTIVE

The purpose of this study was to assess the results of hysteroscopy in postmenopausal women, in which the endometrial thickness as measured by transvaginal ultrasound was ≥ 5 mm, and to compare those findings with the results of endometrial histopathology.

METHODS

A descriptive, retrospective, cross-sectional study was done of 329 postmenopausal women files´, in which transvaginal ultrasound had shown endometrial thickening and who underwent diagnostic hysteroscopy in the Gynecological Endoscopy Sector of Gynecology and Obstetrics Service at Hospital do Servidor Público Estadual "Francisco Morato de Oliveira" (HSPE-FMO), between January 2, 2006 and December 29, 2006.

Women aged 40 years or more, with at least one year of amenorrhea, were considered as being postmenopausal[2].

The study included patients without symptoms and patients with genital bleeding, regardless of hormone therapy. The exclusion criteria were as follows: previously diagnosed gynecologic cancer; any impossibility of performing hysteroscopy or collecting material from the uterine cavity for pathology; and any technical issue which did not allow the biopsy material to be studied.

The age ranged from 40 to 88 years (mean of 63.06 years, standard deviation of 8.56 and median of 63 years). The age of onset of menopause ranged from 33 to 60 years (mean of 49.74 years, standard deviation of 3.90 years and median of 50 years). The postmenopausal period was 1 to 43 years (mean of 13.33 years, standard deviation of 8.96 years and median 12 years). There were 329 patients in the sample, of which 32 patients (9.7%) were using continuous estrogen-progesterone hormone therapy; 35 patients (10.6%) complained of genital bleeding, and 89.4% were asymptomatic.

The Research Ethics Committee of the HSPE-FOM approved this study.

The endometrial echo was measured between the basal layers of the anterior and posterior uterine walls,

in a longitudinal uterine scan. An endometrial echo 5 mm or thicker in any measurement was considered thickened.

Hysteroscopy was performed in an outpatient setting. A Storz Hamou II micro-hysteroscope (4 mm diameter optics, 30 degree angle and 5.0 mm sheath) with a gas channel (CO_2), pressure and flow electronic controls was used. Hysteroscopic findings were characterized based on the Labastida classification (Table 1).

Table 1. Distribution of hysteroscopic findings in 329 patients studied

Findings	n	%
Polyp	183	55.62
Atrophic endometrium	55	16.72
Synechia	26	7.90
Cerebroid-appearance lesion	13	3.95
Myoma	12	3.65
Endometrial hyperplasia	11	3.34
Focal thickening	10	3.04
Proliferative endometrium	8	2.43
Mucus	7	2.13
Cystic atrophy	4	1.22
Total	329	100.00

Endometrial biopsies were done on suspected sites. The lateral, anterior and posterior walls were biopsied when the endometrium had homogeneous characteristics. Guided biopsies were performed in all patients with suspected alterations, and in most women with benign changes. A 3-mm Novak curette coupled to a 20-ml disposable syringe was used. The biopsied material was placed immediately in 10% formaldehyde and sent to the pathology laboratory.

The mean, standard deviation and median of quantitative variables were calculated; the absolute and relative frequencies for qualitative variables were measured. The non-parametric Mann-Whitney test was used to compare two groups (endometrial thickening). The homogeneity between proportions was tested by the χ^2 test or Fisher's exact test. Hysteroscopic images were compared with histology based on efficiency rates. The significance level was 5%.

RESULTS

Endometrial thickness ranged from 6 to 38 mm in 329 sample cases (mean of 10.03 mm, standard deviation of 4.49 and median of 9 mm). The mean (± standard deviation) endometrial thickness in the group with genital bleeding was 14.51 ± 3.72 mm; the same mean for the group without genital bleeding was of 9.5 ± 3.72 mm. There was a significant difference between these two groups ($p < 0.001$).

The mean endometrial thickness for patients on hormone therapy was 11.13 ± 3.99 mm; and for the group not on hormone therapy was 9.91 ± 4.53 mm. There was a significant difference between these two groups ($p < 0.018$). However, there was no association between endometrial cancer or hyperplasia and hormone therapy.

Table 1 shows the hysteroscopic findings in the sample, as follows: polyps in 183 patients (55.62%); atrophic endometrium in 55 (16.72%); synechia in 26 (7.90%); a cerebroid appearance lesion in 13 (3.95%); leiomyomas in 12 (3.65%); endometrial hyperplasia in 11 (3.34%); focal thickening in ten (3.04%); proliferative endometrium in eight (2.43%); mucus in seven (2.13%); and cystic atrophy in four (1.22%). These are hysteroscopic findings with no histological confirmation.

Table 2 shows the hysteroscopic findings according to endometrial thickness. There was a significant difference between each level of endometrial thickening relative to hysteroscopic findings. An atrophic endometrium, myomas and mucus predominated, when the endometrial thickness was 6 to 7 mm. Synechia, focal thickening, a proliferative endometrium and cystic atrophy were more observed when the endometrial thickness varied from 8 to 9 mm. Polyps, a cerebroid appearance and endometrial hyperplasia prevailed when the endometrial thickness was 10 mm or more.

Table 2. Absolute and relative frequencies of hysteroscopic findings according to endometrial thickness

Findings	Endometrial thickness (mm)						p*
	6-7		8-9		≥ 10		
	n	%	n	%	n	%	
Polyp	55	48.2	46	56.1	82	61.6	
Atrophic endometrium	28	24.6	12	14.6	15	11.3	
Synechia	11	9.6	8	9.7	7	5.2	
Cerebroid-appearance lesion	0	0.0	0	0.0	13	9.8	
Myoma	6	5.3	3	3.7	3	2.3	< 0.001
Endometrial hyperplasia	1	0.9	3	3.7	7	5.2	
Focal thickening	1	0.9	4	4.9	5	3.8	
Proliferative endometrium	4	3.5	4	4.9	0	0.0	
Mucus	7	6.1	0	0.0	0	0.0	
Cystic atrophy	1	0.9	2	2.4	1	0.8	
Total	114	100.0	82	100.0	133	100.0	

(*) descriptive probability level in Fisher's exact test

Hysteroscopy findings suggested polyps in 183 patients, of which histology revealed endometrial polyps in 155 patients, atrophic endometrium in 12, endometrium with no atypias in 44, secretory endometrium in three and proliferative endometrium in six. The hysteroscopy was 96.61% sensitive and 99.23% specific for diagnosing polyps. The positive predictive value (PPV) was 84.62% and the negative predictive value (NPV) was 100% (99.26% accuracy). Biopsies were guided but not performed on polyps.

In 55 cases suggesting atrophic endometrium, agreement with the histological diagnosis was found in five cases. In another ten cases, the histological diagnosis was an endometrium with no atypia and in one case there was a secretory endometrium. A biopsy was not performed in 39 women.

In cases suggesting synechia, histology found an endometrium with no atypias in ten cases, atrophic and proliferative endometrium in three cases, and a secretory endometrium and cystic atrophy in one case. A biopsy was not performed in eight cases.

In the 13 cases, in which the endometrium had a cerebroid appearance, histology confirmed adenocarcinoma in 11 cases, and revealed endometrial hyperplasia in the remaining two cases. The sensitivity for endometrial cancer was 100% and the specificity was 99.23%. The PPV was 84.62% and the NPV was 100% (99.26% accuracy).

Cases in which hysteroscopy suggested endometrial hyperplasia, histology confirmed seven of them; two other cases were endometrial atrophy, one case proliferative endometrium and one case, cystic atrophy. Five of seven cases, in which hyperplasia was originally suggested in the group with endometrial thickening ≥ 10 mm, were confirmed by histology. In the 8 to 9 mm endometrial thickness group, two of three suggested cases of hyperplasia in hysteroscopy were confirmed histologically. The only case in which hyperplasia was suggested in the 6 to 7 mm endometrial thickness group, was not confirmed; it was a case of endometrial atrophy. The sensitivity for hyperplasia was 58.33% and the specificity was 98.45%, the PPV was 63.64% and the NPV was 98.07% (96.67% accuracy).

Histological findings in patients with hysteroscopic images suggesting focal thickening were as follows: four cases with atypia-free endometrium, three cases with endometrial hyperplasia, two cases with polyps, and one case with a proliferative endometrium.

Cases in which hysteroscopy suggested a diagnosis of myoma yielded the following histological findings: atypia-free endometrium in three cases, proliferative endometrium in two cases, secretory endometrium in one case, and polyp in one case. Biopsy was not performed in five of these cases. It is relevant to note that biopsies were taken from the endometrium, not from myomas; thus, they were guided but non-directed biopsies.

There is an association between bleeding and polyps, cerebroid lesions and endometrial hyperplasia. The group which presented bleeding had a higher percentage of cases with cerebroid lesions and endometrial hyperplasia, and a lower percentage of cases with polyps, compared to the group with no bleeding (Table 3). Postmenopausal uterine bleeding was present in 11 of 13 patients with cerebroid lesions and in five of 11 patients with endometrial hyperplasia, as seen in hysteroscopy, in nine of 11 cases of histopathologically confirmed endometrial cancer, and in six of nine cases of endometrial hyperplasia. The prevalence of cancer in patients with uterine bleeding was 27.3%, and the prevalence of hyperplasia in these patients was 18.2%. In the sample, 81.8% of cancer patients and 83.3% of patients with hyperplasia were aged over 60 years.

Table 3. Distribution of hysteroscopic findings in 329 patients studied, with or with no postmenopausal bleeding

Findings	Bleeding				p
	Yes		No		
	n	%	n	%	
Polyp	12	34.3	171	58.2	0.007[1]
Atrophic endometrium	2	5.7	53	18.1	0.065[1]
Synechia	1	2.9	25	8.5	0.335[2]
Cerebroid-appearance lesion	11	31.4	2	0.7	< 0.001[2]
Myoma	1	2.9	11	3.7	1.000[2]
Endometrial hyperplasia	5	14.2	6	2.0	0.003[2]
Focal thickening	2	5.7	8	2.7	0.288[2]
Proliferative endometrium	0	0.0	8	2.7	1.000[2]
Mucus	0	0.0	7	2.4	1.000[2]
Cystic atrophy	1	2.9	3	1.0	0.364[2]
Total	35	100.0	294	100.0	

[1] descriptive probability level in χ^2 test; [2]descriptive probability level in Fisher's exact test

DISCUSSION

According to the literature, the cutoff point for postmenopausal endometrial thickness in ultrasound is 4 to 5 mm. It is noteworthy that when the endometrial echo is 5 mm or more, it does not mean that there is endometrial disease; it means that ultrasound is unable to exclude disease. Investigation must, therefore, be supplemented by hysteroscopy[1].

Accorsi Neto et al.[7] studied 58 postmenopausal patients with an endometrial echo ≥ 4 mm, and showed that polyps were the main cause of endometrial thickening in 30 cases (51.7%). Loizzi et al.[8] also showed that polyps were the main lesions which were mistaken for endometrial thickening; this occurred in 23.2% of 155 patients. Litta et al.[9] studied 146 patients and found that polyps and myomas were present in 86 patients (59%), and endometrial cancer was found in 11 patients (7.5%). Campaner et al.[10] applied a 5 mm cutoff point and verified that polyps predominated in 42.1%, followed by endometrial atrophy (12.4%) and synechia (12.4%).

These results are similar to those of other authors. A number of hysteroscopic findings were associated with postmenopausal endometrial thickening, other than polyps (55.62%) and endometrial atrophy (16.72%). There was good agreement between

hysteroscopic and histopathological findings in patients with hyperplasia and endometrial cancer. Guided hysteroscopic biopsies were made, rather than directed biopsies. This certainly explains the fact that histological confirmation of polyps was only attained in 115 of 183 polyps.

Machado, Pina e Matos[11] assessed the accuracy of hysteroscopy in postmenopausal women with vaginal bleeding, and demonstrated that the sensitivity of this method was 85.7% and the specificity was 88.7%. These authors correlated their low diagnostic rates for myomas, neoplasms and endometrial hyperplasia to the use of guided biopsies. Under similar conditions, Garuti et al.[12] observed a sensitivity of 94.2%, specificity of 88.8%, NPV of 96.3% and PPV of 83.1% in 1,500 patients.

Loverro et al.[13] studied 106 women with postmenopausal uterine bleeding to evaluate the agreement between hysteroscopic and histological findings on directed biopsies. These authors noticed that hysteroscopy correctly diagnosed 62 of 67 atrophic endometrium cases (92.5%), 13 of 14 benign alterations (92.9%) and 24 of 25 proven cases of endometrial adenocarcinoma (96%); one case in which hysteroscopy suggested an endometrial polyp was diagnosed histologically as an adenocarcinoma. The specificity of hysteroscopy in separating an atrophic endometrium or a benign condition from cancer was 100%, while the sensitivity was 97%.

Litta et al.[9] studied 220 patients under similar conditions, and concluded that all endometrial cancer and hyperplasia cases were detected by hysteroscopy. Fifty-seven out of 59 atrophy cases were confirmed. All 92 polyps and myomas were confirmed histologically; sensitivity of hysteroscopy was 100%, specificity was 49.6%, PPV was 81.3% and NPV was 100%. Scavuzi et al.[14] found good agreement between hysteroscopy and histology (kappa = 0.61) in 156 patients under similar conditions; the correct diagnosis was made in 13 of 16 cases suggesting cancer, and in seven of 11 cases suggesting hyperplasia. No endometrial cancer case was found in those patients who had an initial hysteroscopic diagnosis of atrophic endometrium, polyps or myomas.

Loizzi et al.[8] studied 155 postmenopausal patients with endometrial thickening ≥ 4 mm. Histology confirmed nine cases of hyperplasia, nine of submucosal myoma and 36 of polyps. There was agreement in 99 of 101 hysteroscopic findings of atrophy; the diagnosis was endometrial hyperplasia in two cases. The sensitivity was 100%; the specificity, 98.9%; the PPV, 97.1%; and the NPV, 100%.

Garuti et al.[15] compared the accuracy of transvaginal ultrasound and the histology of hysteroscopic biopsies in 419 postmenopausal uterine bleeding patients, and found that sensitivity was 95.1%, specificity 54.8%, and PPV 63.7%, using a 4 mm cutoff point. When an 8 mm cutoff point was used, sensitivity was 83.8%, specificity was 81.3% and the PPV 79.4%. In the same year, Bakour et al.[16] used a 4 mm cutoff point and found that sensitivity was 92.9%, specificity 50%, the PPV was 24.1% and the NPV was 97.6%.

According to Giusa-Chiaferi et al.[17], sensitivity at an 8 mm cutoff point was 100% and specificity was 62.3%. According to Grambell Jr. et al.[18], the incidence of hyperplasia or neoplasms was 10 to 20%, when the endometrial echo measured over 10 mm. Litta et al.[9] studied 220 patients and found one patient that had endometrial cancer with an endometrial thickness between 4 and 8 mm, and ten patients with the same condition when the cutoff point was > 8 mm.

Eitan et al.[19] studied 29 patients with endometrial cancer to assess endometrial thickness as measured by ultrasound, which ranged from 5 to 32 mm (mean of 12 mm); the mean in initial stages was 10 mm and the mean in advanced stages was 12 mm. In this study, all patients diagnosed with cancer, and most patients diagnosed with endometrial hyperplasia, were at a cutoff point ≥ 10 mm.

The highest incidence of endometrial cancer is after menopause; the mean age for this is around 60 years. Although patients with postmenopausal uterine bleeding or endometrial thickening in ultrasound (≥ 5 mm) may have benign diseases, an investigation of the uterine cavity with histology of the endometrium is mandatory[20]. In this study, the most frequent findings in patients presenting bleeding were polyps (34.3%), lesions with a cerebroid appearance (31.4%), and endometrial hyperplasia (14.3%). Most patients with a histopathological diagnosis of endometrial cancer presented postmenopausal bleeding (nine of 11 patients), and 83.3% were aged over 60 years.

CONCLUSIONS

This study showed that most postmenopausal women with a thickened endometrium had benign conditions. All patients with endometrial cancer had an endometrial thickness ≥ 10 mm, and most of them had postmenopausal uterine bleeding and were aged 60 years or above. Hysteroscopy with biopsy was a highly accurate method to identify intrauterine abnormalities which were responsible for endometrial thickening, as seen on ultrasound.

Although malignancies were not found when the endometrial echo was < 10 mm thick, a 5 mm cutoff point for indicating hysteroscopy is suggested for

safety reasons and to discard possible endometrial precancerous lesions. Further studies with larger series are required to increase our knowledge of the endometrium in postmenopausal patients.

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