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The value of hysteroscopic biopsy in the diagnosis of endometrial polyps

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Abstract

Several studies have demonstrated that the combination of hysteroscopy with endometrial biopsy is more accurate in differentiating endometrial polyps from endometrial hyperplasia and cancer. However, blind biopsy not always confirms hysteroscopic findings due to high rates of inadequate or insufficient material. The objective of this clinical, prospective, and comparative study was to establish a correlation between the histological results of office-based endometrial biopsies (hysteroscopically guided and blind) with the surgical polypectomy specimens. We evaluated 82 patients with hysteroscopic diagnosis of endometrial polyp, who randomly underwent hysteroscopically guided biopsy or blind biopsy, referred for surgical resection. A total of 36 women (43.9%) underwent hysteroscopically guided biopsy and 46 women (56.1%) underwent blind biopsy. The sensitivity of hysteroscopically guided biopsy for the diagnosis of endometrial polyps ranged between 35.3 and 36.8%, when carried out at the apex and base of the lesion, compared with 29.2% for blind biopsy. Specificity was 33.3, 50, and 60%, respectively, for each biopsy. The positive predictive values were 75, 77.8, and 87.5%, and negative predictive values were 8.3, 14.3, and 8.1% respectively, compared with surgical polypectomy specimens. The office-based endometrial biopsies had low diagnostic accuracy for endometrial polyps compared with surgical polypectomy specimens.

Keywords

Biopsy or diagnosis or methods, hysteroscopy, histology, polyps or anatomy, histology or diagnosis

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Introduction

Endometrial polyps (EP) are neoformations that develop as a result of focal hyperplasia of the endometrial basal layer. They may be sessile or pedunculated, single or multiple, and usually consist of irregularly distributed endometrial glands, stroma, and blood vessels.[1,2]

EP etiopathogenesis is still poorly understood, and no consensus has been reached on their natural history and relevance as pathologic entities. Consequently, there is still controversy regarding the treatment and follow-up of these lesions, particularly in asymptomatic postmenopausal women.[3,4] Several studies have demonstrated that the combination of hysteroscopy with endometrial biopsy is more accurate in differentiating EP from endometrial hyperplasia and endometrial cancer.[5–9] Blind biopsy (BB) not always confirms hysteroscopic findings due to high rates of inadequate or insufficient material and should, therefore, no longer be used in cases of focal endometrial lesions.[10–13] Bettocchi and coworkers[14–16] demonstrated that office hysteroscopy with 5-Fr instruments in combination with hysteroscopically guided biopsy (HGB) can obtain enough material for histology and may be used in several outpatient surgical procedures.

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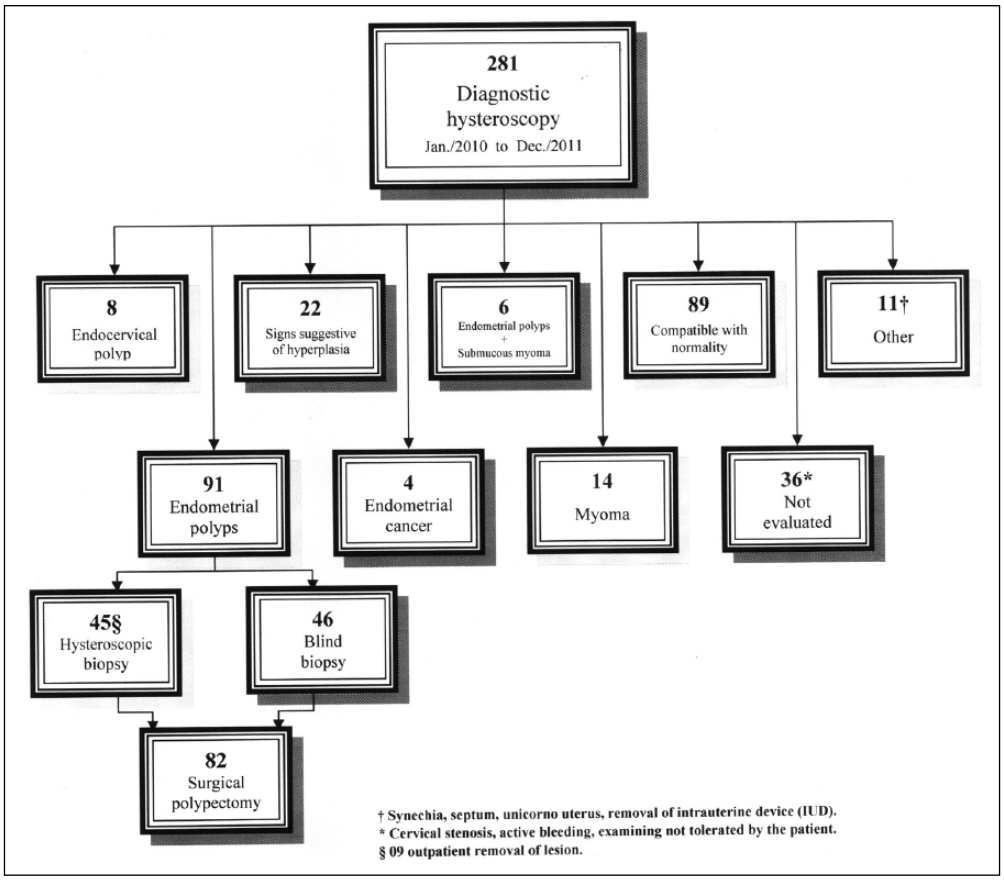

Figure 1. Distribution of the main hysteroscopic findings and number of patients undergoing surgical polypectomy, during the period of January 2010 to December 2011, at the Gynecologic Endoscopy and Family Planning Sector from Botucatu Medical School (FMB/UNESP).

Nonetheless, data suggesting the best type of biopsy to perform or to describe each technique's accuracy in identifying focal intrauterine lesions are still limited. Given that EPs have become the main indication for surgical hysteroscopy, criteria for determining EP malignant potential and indication for surgical removal should be established in order to avoid unnecessary procedures and costs, especially in asymptomatic women.[2] High rates of agreement between histological findings in office-based endometrial biopsies and those in endometrial specimens obtained after surgical hysteroscopy, considered as the gold standard, may indicate the best type of biopsy to perform.

Thus, in order to determine diagnostic accuracy for EP, this preliminary study aimed at assessing the relationship between histological findings obtained after BB and HGB with those in surgical hysteroscopic polypectomy specimens.

Materials and methods

This clinical, prospective, and comparative study included patients attending the Gynecologic Endoscopy and Family Planning Division of the Department of Obstetrics and Gynecology of Botucatu Medical School, São Paulo State University (FMB/UNESP), São Paulo, Brazil. From January 2010 to December 2011, 281 women, with or without clinical symptoms of abnormal uterine bleeding and/or infertility, underwent office hysteroscopy due to endometrial thickening detected by transvaginal ultrasound. Patients with polyps were randomly assigned to either endometrial HGB or BB. HGB was performed under direct visualization with a 5-Fr crocodile forceps, which was used to bite into the endometrium and then closed to get the sample. BB was performed using a 3-mm Novak curette or the Pipelle de Cornier® device (Figure 1). When possible, all lesions were removed during the procedure. All examinations were scheduled in a different hospital unit, so that investigators were not involved in patient scheduling. Four patients were scheduled per day, and randomization was done in such a way that the first and fourth patients of the period underwent HGB, while the second and third underwent BB.

Office hysteroscopy was performed without anesthesia, preferably in the first phase of the menstrual cycle in premenopausal women and at any time after menopause. During HGB, both the base and the apex of the lesion were

biopsied. Hysteroscopy was performed using a 30° lens, with 2.7 or 2.9 mm, coupled to either a simple diagnostic sheath (3.7 mm total diameter) or a 5.2-mm total diameter surgical office sheath (Trophyscope; Karl Storz®, Tuttlingen, Germany), also known as the Bettocchi system. Continuous saline infusion (0.9%) was used for uterus distention at a pressure of 80 mmHg.

Data collected included patient age, body mass index (BMI), smoking status, presence of hypertension and diabetes mellitus, obstetric history, menstrual pattern, and use of hormone replacement therapy or tamoxifen.

Endometrial hyperplasia was suspected when diffuse hypervascularization associated with vascular atypia, characterized by progressive narrowing or abrupt interruption of haphazardly distributed large-caliber vessels, was identified during hysteroscopy. Endometrial cancer, in turn, was suspected when, in addition to the features described above, loss of the architectural integrity of the uterine cavity or presence of amorphous, whitish, and crumbly material was observed.[17,18]

Following histological assessment and exclusion of the cases of atypical hyperplasia and endometrial cancer, 82 patients diagnosed with EPs, with or without cervical polyps, and no other endometrial conditions, were referred to surgical resection. Surgical removal was indicated when office resection was not possible due to polyp size, symptoms refractory to clinical treatment, macroscopically suspicious lesions, presence of endometrial hyperplasia risk factors (advanced age, hypertension, obesity, diabetes, history of gynecological cancer, and use of tamoxifen), and patients' preference.

Surgical hysteroscopy was performed under spinal anesthesia using an 8.8-mm monopolar Karl Storz 26040 SL gynecologic continuous flow resectoscope with 30° Karl Storz Hopkins II optic and a 5-mm semi-curved cutting loop. For uterus distention, sorbitol (3%) was infused through a *Hysteromat Hamou* (series 2633; Karl Storz) with continuous pressure at around 100 mmHg, variable flow, and electronic adjusted vacuum. The power of the electrodes was adjusted to 110 V, around 100 W for cutting and 80 W for coagulation with blend 1 monopolar current. For histological analysis, BB and HGB samples and surgical polypectomy specimens were fixed in 10% formaldehyde and sent to the FMB/UNESP Laboratory of Clinical Pathology.

For data analysis, measures of location and variability were calculated. Mean, standard deviation, median, and minimum or maximum values for quantitative variables, and absolute frequency and percentage for qualitative variables were estimated. Normally distributed and not normally distributed quantitative variables were compared using the Student *t*-test and the nonparametric test of Mann–Whitney, respectively. Qualitative variables were analyzed using the test of Goodman for contrasts among multinomial populations.[19,20] Sensitivity, specificity, and predictive values were calculated for the correlation of BB and HGB histological findings with those in surgical specimens.[21] Data analysis was performed using SPSS for Windows, V.15.0 with significance level set at 5%. This study was approved by the institution's Research Ethics Committee, and written informed consent was obtained from all patients.

Results

Of the 82 patients diagnosed with EP referred to surgical polypectomy, 36 (43.9%) underwent HGB and 46 (56.1%) underwent BB. In nine patients of the HGB group, it was possible to remove the entire lesion during office hysteroscopy (Figure 1). Mean patient age was 54 and 59 years, and the proportion of postmenopausal women was 59.4% and 74% in groups HGB and BB, respectively ($p > 0.05$). No differences in parity, BMI, use of hormone replacement therapy, and associated diseases were observed between groups (Table 1).

The most frequent EP clinical manifestation in the HGB group was increased menstrual flow (30.6% of cases), whereas in the BB group, it was postmenopausal bleeding (34.8% of cases). Asymptomatic women, who underwent hysteroscopic examination because of incidental findings on routine ultrasound scans, accounted for 33% and 39% of the cases in groups HGB and BB, respectively (Table 2).

BB diagnosed only 30.4% of EPs, while HGB at the apex and at the base of lesions diagnosed 36.1% and 30.5% of EP cases, respectively ($p > 0.05$). In addition to EP, BB diagnosed two cases of simple endometrial hyperplasia without atypia and two cases of complex hyperplasia with atypia. One of the cases of hyperplasia without atypia was later proved to be an EP and the other an endometrial adenocarcinoma. In one of the cases of hyperplasia with atypia, endometrial adenocarcinoma was diagnosed after hysterectomy. No case of hyperplasia was diagnosed by HGB. The other findings obtained from each type of biopsy are shown in Table 3.

The sensitivity of office hysteroscopy alone for diagnosing EP was 86.1–100%. HGB diagnostic sensitivity, specificity, positive and negative predictive values were 35.3, 33.3, 75, and 8.3%, respectively, at the lesion apex, and 36.8, 50, 77.8, and 14.3%, respectively, at the lesion base. BB showed a sensitivity of 29.2% and specificity of 60%, with positive and negative predictive values of 87.5% and 8.1%, respectively, when compared with surgical polypectomy. The rates of hyperplasia and cancer associated with polyps were 1.2% and 2.4%, respectively (Table 3).

Discussion

The pathogenesis of EPs, a common cause of postmenopausal bleeding, is unclear, and their management is still

Table 1. Distribution of epidemiological and clinical characteristics of 82 patients diagnosed with endometrial polyps undergoing hysteroscopically guided biopsy ($n = 36$) and blind biopsy ($n = 46$).

Variable	Hysteroscopically guided biopsy ($n = 36$)	Blind biopsy (n = 46)	p-value**
Age (years)[a]	54 (35; 75)	59 (24; 72)	>0.05
BMI (kg/m^2)[b]	30.7 ± 5.9	32.2 ± 5.8	>0.05
Number of pregnancies[a]	3 (0; 8)	3 (0; 9)	>0.05
Parity[a]	3 (0; 7)	2 (0; 9)	>0.05
Abortions[a]	0 (0; 3)	0 (0; 2)	>0.05
Cesarean sections[a]	1 (0; 3)	1 (0; 4)	>0.05
Hypertension, *n* (%)	21 (58.3)	29 (63.0)	>0.05
Diabetes mellitus, *n* (%)	5 (13.9)	13 (28.3)	>0.05
Dyslipidemia, *n* (%)	2 (5.6)	7 (15.2)	>0.05
Hypothyroidism, *n* (%)	2 (5.6)	2 (4.3)	>0.05
Smoking, *n* (%)	4 (11.1)	9 (19.6)	>0.05
HRT use, *n* (%)	2 (5.6)	6 (13.0)	>0.05
Breast cancer, *n* (%)	1 (2.8)	3 (6.5)	>0.05

BMI: body mass index; HRT: hormone replacement therapy.
n (%; test of Goodman).
[a]Median and minimum and maximum values between parentheses (Mann–Whitney test).
[b]Mean ± standard deviation of the variables according to the group (Student's *t*-test).
**Significant difference if $p < 0.05$.

Table 2. Distribution of the main clinical manifestations of 82 patients diagnosed with endometrial polyps undergoing hysteroscopically guided biopsy ($n = 36$) and blind biopsy ($n = 46$).

Variable	Hysteroscopically guided biopsy ($n = 36$)	Blind biopsy ($n = 46$)	p-value*
Increased menstrual flow, *n* (%)	11 (30.6)	8 (17.4)	>0.05
Frequent menses, *n* (%)	3 (8.3)	2 (4.3)	>0.05
Postmenopausal bleeding, *n* (%)	9 (25.0)	16 (34.8)	>0.05
Asymptomatic, *n* (%)	12 (33.3)	18 (39.1)	>0.05
Cervical polyp, *n* (%)	2 (5.6)	9 (19.6)	**<0.05**
Infertility, *n* (%)	0 (0.0)	2 (4.3)	>0.05

*Significant difference if $p < 0.05$ (Goodman test).

the object of debate. Normally associated with hyperestrogenism, EP can arise even in an atrophic or inactive endometrium and, in this environment, develop into carcinoma.[22] The reported incidence of malignancy in women with EP ranges between 0% and 4.8%.[23–26]

To date, reliable clinical parameters indicating the best approach for treating EP in asymptomatic women are still not available.[17] Considering EP frequent diagnosis and low malignancy rate, some authors advocate the removal of polyps in only symptomatic cases (infertility or vaginal bleeding), while others recommend the systematic removal of all EPs.[3,4,27]

Removing polyps only in cases of vaginal bleeding may exclude the possibility of diagnosing endometrial cancer prior to its clinical manifestation, while the systematic removal of all EPs results in unnecessary additional costs that place a greater burden on healthcare, particularly in public systems. Thus, discussing the establishment of criteria for optimal EP management by assessing the effectiveness of the endometrial biopsy techniques most used in clinical practice is highly justifiable.

In this study, BB and HGB at the apex and at the base of the lesion showed low sensitivity for diagnosing EP, in agreement with other reports. In previous studies, BB showed a sensitivity between 8% and 46%, a positive predictive value between 31% and 100%, and negative predictive value between 7% and 58%.[4,13,28,29] Furthermore, ultrasound-guided biopsy has been shown to not improve the diagnostic potential of BB, as observed with HGB in this study.[30,31]

Despite allowing direct visualization of the lesion, HGB as conducted in this study yielded inadequate or insufficient material in 48.6% of the cases. In addition, BB does not often precisely reach focal endometrial lesions, which associated with the softened nature of the polyp hinders the uptake of representative samples, justifying the high rates of inappropriate or insufficient material.[13]

HGB at both the apex and the base of the lesion demonstrated low specificity in differentiating polyps from

Table 3. Distribution of the histological results, sensitivity, specificity, PPV, and NPV for the diagnosis of endometrial polyp according to the type of biopsy performed in comparison with the surgical polypectomy considered as the *gold standard* ($n = 82$).

Variable	Hysteroscopically guided biopsy (apex; $n = 36$)	Hysteroscopically guided biopsy (base; $n = 36$)	Blind biopsy ($n = 46$)	Surgical polypectomy[a] ($n = 82$)
Proliferative endometrium, *n* (%)	1 (2.8)	1 (2.8)	2 (4.3)	5 (6.1)
Secretory endometrium, *n* (%)	2 (5.5)	1 (2.8)	3 (6.5)	2 (2.4)
Atrophic endometrium, *n* (%)	3 (8.3)	2 (5.5)	5 (10.9)	10 (12.2)
Endometrial polyp, *n* (%)	13 (36.1)	11 (30.5)	14 (30.4)	77 (93.9)
Hyperplasia without atypia, *n* (%)	0 (0.0)	0 (0.0)	2 (4.3)	0 (0.0)
Atypical hyperplasia, *n* (%)	0 (0.0)	0 (0.0)	2 (4.3)	1 (1.2)
Adenocarcinoma of the endometrium, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.4)
Insufficient material, *n* (%)	16 (44.4)	19 (52.7)	22 (47.8)	–
Other,[b] *n* (%)	1 (2.8)	2 (5.5)	1 (2.2)	6 (7.3)
Sensitivity (%)	35.3	36.8	29.2	–
Specificity (%)	33.3	50.0	60.0	–
PPV (%)	75.0	77.8	87.5	–
NPV (%)	8.3	14.3	8.1	–

PPV: positive predictive value; NPV: negative predictive value.
[a]Gold standard.
[b]Mucus, ectocervix fragments, mixed endometrium, tubal metaplasia, fibroids, and adenomyosis.

endometrial hyperplasia and failed to diagnose endometrial cancer, despite the small number of cases. The few cases of hyperplasia observed in this study were diagnosed by BB which has already been demonstrated effectively to detect diffuse intrauterine alterations.[11,32]

It is noteworthy that in this study, HGB was performed using a 5-Fr forceps to bite and close into the endometrium, while the hysteroscope remained inside the uterine cavity. This is not in accordance with Bettocchi et al., who suggested that to improve the amount of tissue obtained, the forceps should be placed with jaws open and then pushed against the lesion to detach the surrounding endometrium pulling the entire hysteroscope out of the uterine cavity without pulling the tip of the instrument back into the channel. This so-called grasp technique seems to be more satisfactory in obtaining sufficient material for histology.[14]

The rates of atypia (1.2%) and malignancy (2.4%) observed in this study are in agreement with those reported in the literature that range from 1% to 3.1% and 0.8% to 3.2%, respectively.[3,33,34] Nonetheless, the rates of hyperplasia and malignancy in EP may be higher, depending on the population studied. Previous studies have found hyperplasia without atypia associated with EP in 11–25% of the cases, and there are reported series with up to 13% of malignant polyps.[24,33–36] Furthermore, the rate of hyperplasia and malignancy in polyps may be similar in women with (3.2%) and without bleeding (3.9%).[27]

The usefulness of clinical factors in predicting malignant changes in polyps is at the center of an ongoing debate. The reported risk factors for malignancy in EPs are the same as those associated with endometrial cancer, notably advanced age, nulliparity, early menarche, late menopause, obesity, hypertension, diabetes, and use of tamoxifen.[26,34,37–39] Polyp size has also been suggested as a risk factor for atypia in EPs, as polyps larger than one-third of the endometrial cavity appear to be more susceptible to bleeding and malignancy.[2,24,40] Some studies have shown that despite being significantly related to EPs, hypertension, obesity, and diabetes lose significance when multivariate logistic regression adjusted for age is performed, indicating that postmenopausal status and advancing age are the only independent risk factors for malignancy of polyps.[41–43]

Thus, given that no reliable clinical parameters are available, and that the accuracy of endometrial biopsies for diagnosing focal intrauterine lesions is low, the removal of EPs larger than one-third of the uterine cavity is recommended in elderly patients (>60 years) and in those with postmenopausal bleeding who are at an increased risk of malignancy.[17,40,43] Patients with risk factors for malignancy may be considered at intermediate risk and should be appropriately followed up according to each center's routine. To minimize costs, outpatient excisional biopsy of smaller polyps should be performed using techniques that permit the complete removal of the entire lesion such as the grasp technique, and the cases of polyps larger than the cervical ostium and diffuse polyposis should undergo removal with an operative resectoscope.

Conclusion

This preliminary study demonstrated that office-based biopsies (BB and HGB) had low diagnostic accuracy for EPs when compared with surgical polypectomy specimens. The use of an adequate technique for HGB may further improve the outcomes achieved.

Executive summary

- Several studies have demonstrated that the combination of hysteroscopy with endometrial biopsy is more accurate in differentiating EP from endometrial hyperplasia and endometrial cancer. However, BB not always confirms hysteroscopic findings due to high rates of inadequate or insufficient material.
- Despite allowing direct visualization of the lesion, HGB may also yield inadequate or insufficient material if an improper technique is applied such as using a 5-Fr forceps to bite and close into the endometrium, while the hysteroscope remains inside the uterine cavity.
- In this clinical, prospective, and comparative study conducted in a tertiary public hospital or university teaching center, 82 patients with hysteroscopic diagnosis of EP randomly underwent HGB (43.9%) or BB (56.1%) previously to surgical resection.
- The sensitivity of HGB for the diagnosis of EPs ranged between 35.3% and 36.8%, when carried out at the apex and base of the lesion, compared with 29.2% for BB. Specificity was 33.3, 50, and 60%, respectively, for each biopsy. The positive predictive values were 75, 77.8, and 87.5%, and negative predictive values were 8.3, 14.3, and 8.1%, compared with surgical polypectomy specimens. The rates of hyperplasia and cancer related to polyps were 1.2% and 2.4%.
- The reported risk factors for malignancy in EPs are the same as those associated with endometrial cancer. Polyp size has also been suggested as a risk factor for atypia in EPs. However, some studies have shown that postmenopausal status and advancing age are the only independent risk factors for malignancy of polyps.
- To date, reliable clinical parameters indicating the best approach for treating EP in asymptomatic women are still not available. Considering EP frequent diagnosis and low malignancy rate, discussing the establishment of criteria for optimal EP management by assessing the effectiveness of the endometrial biopsy techniques is highly justifiable.
- To improve the amount of tissue obtained during HGB, Bettocchi et al. suggested that the forceps should be placed with jaws open and then pushed against the lesion to detach the surrounding endometrium pulling the entire hysteroscope out of the uterine cavity without pulling the tip of the instrument back into the channel. This so-called grasp technique seems to be more satisfactory in obtaining sufficient material for histology.
- Given that no reliable clinical parameters are available, and that the accuracy of endometrial biopsies for diagnosing focal intrauterine lesions is low, the removal of EPs larger than one-third of the uterine cavity is recommended in elderly patients (>60 years) and in those with postmenopausal bleeding.
- Patients with clinical risk factors for malignancy may be considered at intermediate risk and should be appropriately followed up according to each center's routine.
- Outpatient excisional biopsy of smaller polyps should be performed using techniques that permit the complete removal of the entire lesion, and the cases of polyps larger than the cervical ostium and diffuse polyposis should undergo removal with an operative resectoscope.

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