Research Article

Accuracy of Preoperative Endometrial Sampling for the Detection of Endometrial Pathology: a Retrospective Study

Akurasi dari Pra-operatif Sampel Endometrium untuk Mendeteksi Patologi Endometrium: Studi Retrospektif

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Abstract

Objective: To investigate the accuracy of endometrial sampling in the diagnosis of endometrial pathology and the need of intra-operative frozen section.

Methods: One hundred forty women who underwent endometrial sampling followed by hysterectomy between 2011 and 2014 were included in this study. Data were retrieved from patient files and pathology archives in Department of Obstetrics and Gynecology, Jose R. Reyes Memorial Medical Center, Manila, Philippines.

Results: There were 25 patients with malignancy but endometrial sampling detected only 22 of them. The endometrial sampling sensitivity and specificity for detecting cancer were 88% and 100%, respectively with negative and positive predictive values of 97.5% and 100%, respectively. In 3 patients, the endometrial sampling failed to detect malignancy; 1 patient had a preoperative diagnosis of complex hyperplasia with atypia, 1 patient had complex hyperplasia without atypia and 1 patient had adenofibroma. A total of eighty patients had benign findings. There were fifty-three cases with finding of proliferative endometrium and twenty-seven were secretory. Twenty-three (55.0%) and 11 (39.0%) cases were confirmed by the hysterectomy specimen, respectively. The sensitivity of endometrial sampling in detecting benign samples was 76.0% and the specificity reached up to 83.0%. The histopathology result of the other fourteen cases were reported of having atrophy, twelve cases were reported of having endometrial hyperplasia, four with basal endometrium, four with endometrial polyp and one with adenomyosis.

Conclusion: Outpatient endometrial biopsy has a high overall accuracy in diagnosing endometrial cancer when the specimen obtained is sufficient. A positive test result is more accurate for ruling in disease than a negative test result is for ruling it out. However, the diagnosis should be confirmed by frozen section in patients with complex hyperplasia and adenofibroma.

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Keywords: abnormal uterine bleeding, endometrial hyperplasia, endometrial sampling, frozen section, pipelle

Abstrak

***Tujuan**: Untuk menyelidiki keakuratan pengambilan sampel endometrium dalam mendiagnosis patologi endometrium dan kebutuhan yang memerlukan teknik potong beku selama operasi.*

***Metode**: Seratus empat puluh perempuan yang menjalani pengambilan sampel endometrium diikuti oleh histerektomi antara 2011-2014 dilibatkan dalam penelitian ini. Data diambil dari file pasien dan arsip patologi.*

***Hasil**: Terdapat 25 pasien dengan keganasan, namun endometrium sampel hanya mampu mendeteksi 22 dari mereka. Sensitivitas dan spesifisitas dari pengambilan sampel endometrium mendeteksi kanker adalah masing-masing 88% dan 100%, dengan nilai duga negatif dan positif masing-masing sebesar 97,5% dan 100%. Pada 3 pasien, pengambilan sampel endometrium gagal mendeteksi keganasan; 1 pasien memiliki diagnosis preoperatif kompleks hiperplasia dengan atipia, 1 pasien memiliki kompleks hiperplasia tanpa atipia dan 1 pasien memiliki adenofibroma. Sebanyak delapan puluh pasien memiliki temuan jinak. Ada 53 kasus dengan temuan proliferasi endometrium dan 27 yang sekretori. Masing-masing sebanyak 23 (55,0%) dan 11 (39,0%) dikonfirmasi oleh spesimen histerektomi. Sensitivitas sampling endometrium dalam mendeteksi sampel jinak adalah 76,0% dan spesifisitas adalah 83,0%. Hasil histopatologi dari 14 kasus lain dilaporkan memiliki atrofi, 12 kasus dilaporkan memiliki hiperplasia endometrium, 4 dengan basal endometrium, 4 memiliki polip endometrium dan 1 memiliki adenomiosis.*

***Kesimpulan**: Rawat jalan biopsi endometrium memiliki akurasi keseluruhan tinggi dalam mendiagnosis kanker endometrium ketika spesimen yang diperoleh sudah cukup. Hasil tes positif lebih akurat untuk mendiagnosis suatu penyakit daripada suatu hasil tes negatif untuk mengesampingkan suatu penyakit. Namun, diagnosis harus dikonfirmasi oleh potong beku pada pasien dengan kompleks hiperplasia dan adenofibroma.*

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***Kata kunci**: hiperplasia endometrium, perdarahan uterus abnormal, pipelle, potong beku, sampel endometrium*

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INTRODUCTION

Abnormal uterine bleeding (AUB) accounts for 20% of visits to the gynecologist. It is defined as any variation of bleeding outside from normal menstrual cycle that includes change in regularity, frequency, duration of flow, and amount of blood loss. Several common pathological conditions causing abnormal vaginal bleeding are leiomyomas, endometrial polyps, and adeno-myosis. Other less frequent conditions are endometritis and uterine cancers.[1]

Endometrial pathology has been identified and diagnosed using several methods. Endometrial sampling has gained popularity as an alternative diagnostic tool compared with more invasive procedures, such as fractional dilatation and curettage (D&C).[2]

The morphological appearance of atypical endometrial hyperplasia and well-differentiated endometrial carcinoma on biopsy specimen presents a major challenge to pathologists.[3] When a Pipelle endometrial biopsy or curettage specimen can be diagnosed as atypical hyperplasia, there is a risk of concomitant invasive carcinoma in the uterus. Seven to fifty percent (7-50%) of women with endometrial hyperplasia with cytological atypia were found to have concomitant carcinoma in subsequent hysterectomy specimens.[4] Exclusion of cancer in an atypical hyperplasia finding on biopsy is a difficult challenge for the gynecologist.

Hysterectomy is the most frequently performed surgery in gynecology. When it performed for benign indication, frozen section should still be kept doing if there is suspicion of malignancy in the gross specimen in spite of a negative preoperative biopsy.

Several studies had been performed to evaluate the accuracy of endometrial biopsy in identifying the cause of AUB and they showed variation of results.[5-7] According to this discrepancy, we conducted this study to compare the accuracy of preoperative endometrial sampling for the detection of endometrial pathology with postoperative hysterectomy specimen in local settings.

METHODS

This was a retrospective cohort study design involving chart review of patients who underwent endometrial sampling and were treated with hysterectomy in Department of Obstetrics and Gynecology, Jose R. Reyes Memorial Medical Center, Manila, Philippines from January 2011 to December 2014. Clinical and pathological information were reviewed and obtained from patient charts to complete the desired sample size for the study. All collected data were recorded, encoded, and presented in tables. We reviewed the charts of 140 patients who were qualified. Accuracy of endometrial sampling and hysterectomy specimen were determined by computing for the sensitivity, specificity, PPV, and NPV for each diagnostic modality by comparing the preoperative results with the final histopathology findings.

Inclusion criteria included all women with AUB and concomitant gynecological pathology who underwent endometrial sampling and were treated by hysterectomy within a year of the diagnosis. Exclusion criteria were all women who presented with AUB due to cervical pathology and patients who underwent hysterectomy more than a year of the diagnosis.

Review of charts, histopathological results of endometrial sampling, and final histopathological results were gathered from the medical records and Pathology Department from January 2011 to December 2014.

All the statistical tests were performed in SPSS version 20.0. We considered the result significantly if p-values less than 0.05.

RESULTS

A total of 140 women were included in the study, with mean age of 47.9 years old (ranging from 28 to 70 years old) and mean gravidity of 2.8 (ranging from 0 to 11). Forty-two (30.0%) were post-menopausal women who were 50 years old or older.

Myoma was the most common indication for hysterectomy, as reported by 47 (33.6%) patients, followed by AUB (n=33, 23.6%), and endometrial carcinoma (n=22, 15.7%). Less common reasons were post-menopausal bleeding (n=8, 5.7%) and pelvic organ prolapse (n=1, 0.7%).

The preoperative results of endometrial sampling and the final pathological diagnosis were described on Table 1.

Table 1. Concordance Rate of Endometrial Biopsy and Hysterectomy Specimen Histopathology

Finding	Pipelle Biopsy N (%)	Hysterectomy Specimen N (%)	Concordance N (%)
Malignant			
Adenocarcinoma	21 (15.0)	23 (16.4)	21 (15.0)
Malignant Mixed Müllerian Tumor (MMMT)	0 (0)	1 (0.7)	0 (0)
Serous Carcinoma	1 (0.7)	1 (0.7)	1 (0.7)

Finding	Pipelle Biopsy N (%)	Hysterectomy Specimen N (%)	Concordance N (%)
Benign			
Proliferative	42 (30.0)	53 (37.9)	23 (16.4)
Secretory	28 (20)	27 (19.3)	11 (7.9)
Endometrial hyperplasia			
Complex hyperplasia with atypia	2 (1.4)	1 (0.7)	0 (0)
Complex hyperplasia without atypia	2 (1.4)	0 (0)	0 (0)
Simple hyperplasia with atypia	1 (0.7)	1 (0.7)	0 (0)
Simple hyperplasia without atypia	15 (10.7)	10 (7.1)	4 (2.9)
Adenofibroma	1 (0.7)	0 (0)	0 (0)
Adenomyosis	1 (0.7)	1 (0.7)	1 (0.7)
Atrophic	12 (8.6)	14 (10)	6 (4.3)
Basal Endometrium	1 (0.7)	4 (2.9)	1 (0.7)
Endometrial polyp	5 (3.6)	4 (2.9)	1 (0.7)
Tissue Insufficiency	8 (5.7)	0 (0)	0 (0)

Of the twenty-three (16.4%) cases confirmed to have adenocarcinoma by hysterectomy specimen, 21 cases were correctly diagnosed by endometrial biopsy. One case of serous carcinoma was also correctly diagnosed by endometrial biopsy. One case of Malignant Mixed Müllerian Tumor (MMMT) was missed by endometrial biopsy.

For the benign cases, 53 (37.9%) cases were read as proliferative endometrium in the final specimen. Only 23 out of 42 cases were initially diagnosed by endometrial biopsy matched the result of hysterectomy specimen. Twenty-seven (19.3%) were confirmed secretory cases, but only 11 out of 28 cases were initially diagnosed secretory cases as confirmed by hysterectomy specimen. None of the proliferative and secretory reading by endometrial biopsy were interpreted as cancer on the final hysterectomy specimen.

Two cases of complex hyperplasia with atypia were diagnosed by endometrial biopsy, which on hysterectomy specimen was found to have proliferative endometrium and adenocarcinoma. Two cases of complex hyperplasia without atypia were diagnosed by endometrial biopsy; however, they were not confirmed at hysterectomy. One of them turned out to be simple hyperplasia on hysterectomy specimen and the other one was adenocarcinoma. Another case was accurately diagnosed as simple hyperplasia both by sampling and hysterectomy specimen. One case of simple hyperplasia with atypia was initially diagnosed by endometrial biopsy; it was confirmed by hysterectomy section yet. Of the 15 cases of simple hyperplasia without atypia diagnosed by endometrial biopsy, four cases were confirmed by hysterectomy section. There were other six cases of simple hyperplasia without atypia as reported by hysterectomy specimen which endometrial biopsy failed to diagnose initially.

There were 71 patients with benign endometrial pathologies diagnosed by endometrial biopsy, but only 61 (85.9%) cases were confirmed by hysterectomy specimen results. Hysterectomy specimen showed that among those 10 patients, five had atrophy, two had simple hyperplasia without atypia, one had endometrial polyp, one had basal endometrium, and one had simple hyperplasia with atypia.

All the 22 patients with malignancy diagnosed by endometrial biopsy remained the same by final pathology. Endometrial biopsy failed to diagnose the other three cases of malignancy. Complex hyperplasia with and without atypia were the biopsy diagnoses of the two adenocarcinoma cases; while, adenofibroma was the initial diagnosis of the patient with MMMT.

Table 2. Kappa, Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value of Endometrial Biopsy Compared with Hysterectomy Specimen

Findings	N (%)	Kappa	Sensitivity	Specificity	PPV	NPV
Malignant	25 (17.9)	0.923*	22/25 (88.0%)	115/115 (100.0%)	22/22 (100.0%)	115/118 (97.5%)
Adenocarcinoma	23 (16.4)	0.946*	21/23 (91.3%)	117/117 (100.0%)	21/21 (100.0%)	117/119 (98.3%)
Malignant Mixed Müllerian Tumor (MMMT)	1 (0.7)	0.000	0/1 (0%)	139/139 (100.0%)	0/0	139/140 (99.3%)
Serous carcinoma	1 (0.7)	1.000*	1/1 (100.0%)	139/139 (100.0%)	1/1 (100.0%)	139/139 (100.0%)
Benign	80 (57.1)	0.585*	61/80 (76.3%)	50/60 (83.3%)	61/71 (85.9%)	50/69 (72.5%)
Proliferative	53 (37.9)	0.225*	23/53 (43.4%)	68/87 (78.2%)	23/42 (54.8%)	68/98 (69.4%)
Secretory	27 (19.3)	0.253*	11/27 (40.7%)	96/113 (85%)	11/28 (39.3%)	96/112 (85.7%)
Others	35 (25.0)					
Endometrial hyperplasia	12 (8.6)	0.370*	7/12 (58.3%)	115/128 (89.8%)	7/20 (35.0%)	115/120 (95.8%)
Complex hyperplasia with atypia	1 (0.7)	-0.010	0/1 (0%)	137/139 (98.6%)	0/2 (0%)	137/138 (99.3%)
Complex hyperplasia without atypia	0 (0)	0.000	0/0	138/140 (98.6%)	0/2 (0%)	138/138 (100.0%)
Simple hyperplasia with atypia	1 (0.7)	-0.007	0/1 (0%)	138/139 (99.3%)	0/1 (0%)	138/139 (99.3%)
Simple hyperplasia without atypia	10 (7.1)	0.256*	4/10 (40.0%)	119/130 (91.5%)	4/15 (26.7%)	119/125 (95.2%)
Adenofibroma	0 (0)	0.000	0/0	139/140 (99.3%)	0/1 (0%)	139/139 (100.0%)
Adenomyosis	1 (0.7)	1.000*	1/1 (100.0%)	139/139 (100.0%)	1/1 (100.0%)	139/139 (100.0%)
Atrophic	14 (10)	0.407*	6/14 (42.9%)	120/126 (95.2%)	6/12 (50.0%)	120/128 (93.8%)
Basal endometrium	4 (2.9)	0.393*	1/4 (25.0%)	136/136 (100%)	1/1 (100.0%)	136/139 (97.8%)
Endometrial polyp	4 (2.9)	0.179*	1/4 (25.0%)	132/136 (97.1%)	1/5 (20.0%)	132/135 (97.8%)
Tissue insufficiency	0 (0)	0.000	0/0	132/140 (94.3%)	0/8 (0%)	132/132 (100.0%)

The endometrial sampling sensitivity and specificity of detecting malignant cancer were 88.0% [22/25] and 100.0% [115/115], with negative and positive predictive values of 100.0% [22/22], and 97.5% [115/118], respectively (Table 2).

On the remaining 47 patients that biopsy failed to detect as malignancy or benign pathologies, three cases were confirmed to be malignancy (two adenocarcinoma cases and one case of MMMT), 19 confirmed with benign cases (17 proliferative and two secretory), and 25 others (nine cases of atrophy, eight cases of simple hyperplasia without atypia, three cases of basal endometrium, three cases of endometrial polyp, one case of adenomyosis, and one case of complex hyperplasia with atypia).

Pipelle biopsy had a very good agreement [K=0.923, p<0.001] in the diagnosis of malignant cancer. Specifically, it had very good agreement [K=0.946, p<0.001] in diagnosis of adenocarcinoma with sensitivity and specificity of 91.3% and 100.0%, respectively, with positive predictive value of 100.0% and negative predictive value of 98.3%. It also had very good agreement [K=1.000, p<0.001] in diagnosis of serous carcinoma with sensitivity, specificity, positive predictive value and negative predictive value of 100.0% for all results. However, it had poor agreement [K=0.000, p=1.000] in the diagnosis of MMMT in 1 patient, which the endometrial sampling failed to detect malignancy of adenofibroma on a 64-year old woman with postmenopausal bleeding.

For benign samples, Pipelle biopsy had moderate agreement [K=0.585, p<0.001] with hysterectomy specimen results, having sensitivity and specificity of 76.3% and 83.3%, respectively. Specifically, proliferative [K=0.225, p=0.007] and secretory [K=0.253, p=0.003] of benign cases had fair agreement with hysterectomy specimen results.

Other findings showed that Pipelle biopsy had fair agreement in diagnosing atrophy [K=0.407, p<0.001], basal endometrium [K=0.393, p<0.001]; however, it described poor agreement in the diagnosis of endometrial polyp [K=0.179, p<0.019]. Among the endometrial hyperplasia, Pipelle biopsy showed significant agreement [K=0.256, p=0.002] with hysterectomy specimen results only in the diagnosis of simple hyperplasia without atypia. The Pipelle biopsy showed no significant agreement with hysterectomy specimen results in the diagnosis of other endometrial hyperplasia, such as simple hyperplasia with atypia [K=-0.007, p=0.932], complex hyperplasia with atypia [K=-0.010, p=0.904] and complex hyperplasia without atypia [K=0.000, p=1.000]. Likewise, the Pipelle biopsy showed no significant agreement with hysterectomy specimen results in the diagnosis of adenofibroma [K=0.000, p=1.000] and tissue insufficiency [K=0.000, p=1.000].

Twenty patients diagnosed with endometrial hyperplasia through Pipelle biopsy were confirmed to have endometrial hyperplasia only in seven patients, leading to PPV of 35.0%. The remaining 13 patients were confirmed to have proliferative (n=8), adenocarcinoma (n=2), basal endometrium (n=1) and secretory (n=2). All descriptions were shown on Table 3.

Eight specimens were found to have tissue adequacy. Gravidity (p=0.127) and menopausal status (p=0.299) did not determine sample adequacy of Pipelle biopsy.

Table 3. Confirmation of Hysterectomy Specimen in Patients with Initial Endometrial Hyperplasia through Endometrial Biopsy

Case	Age (years old)	Indication	Pipelle Biopsy	Hysterectomy specimen
1	57	Endometrial hyperplasia	Complex hyperplasia with atypia	Adenocarcinoma
2	47	Endometrial hyperplasia	Complex hyperplasia with atypia	Proliferative
3	51	Endometrial hyperplasia	Complex hyperplasia without atypia	Simple hyperplasia without atypia
4	49	Endometrial hyperplasia	Complex hyperplasia without atypia	Adenocarcinoma
5	47	Endometrial hyperplasia	Simple hyperplasia with atypia	Simple hyperplasia without atypia
6	44	Endometrial hyperplasia	Simple hyperplasia without atypia	Secretory
7	52	Endometrial hyperplasia	Simple hyperplasia without atypia	Secretory
8	43	AUB	Simple hyperplasia without atypia	Proliferative
9	44	AUB	Simple hyperplasia without atypia	Proliferative
10	47	Endometrial hyperplasia	Simple hyperplasia without atypia	Proliferative
11	65	Ovarian Cyst	Simple hyperplasia without atypia	Proliferative
12	50	Endometrial hyperplasia	Simple hyperplasia without atypia	Proliferative
13	40	Myoma	Simple hyperplasia without atypia	Proliferative
14	40	Endometrial hyperplasia	Simple hyperplasia without atypia	Proliferative
15	55	Endometrial hyperplasia	Simple hyperplasia without atypia	Complex hyperplasia with atypia
16	48	AUB	Simple hyperplasia without atypia	Basal endometrium
17	39	Endometrial hyperplasia	Simple hyperplasia without atypia	Simple hyperplasia without atypia
18	51	Endometrial hyperplasia	Simple hyperplasia without atypia	Simple hyperplasia without atypia
19	45	Endometrial hyperplasia	Simple hyperplasia without atypia	Simple hyperplasia without atypia
20	44	Endometrial hyperplasia	Simple hyperplasia without atypia	Simple hyperplasia without atypia

DISCUSSION

Abnormal uterine bleeding has been the most common complaint of women during reproductive years and post-menopausal life. There are various benign reasons for AUB. However, uterine bleeding is the most common sign of endometrial cancer.

Endometrial sampling with Pipelle is cost effective and a safe procedure; it is widely used in the investigation of perimenopausal and post-menopausal women with AUB. We take only a few minutes to perform the procedure with Pipelle so that it is the most convenient and best tolerated. Besides, this procedure causes less pain.[8] In a local study by L. Co, et al. in 2000, Pipelle endometrial biopsy instrument was an effective office device for evaluating patients with AUB because it was associated with less pain, better specimen yield with similar histologic findings (100%) as the standard curettage.[9] Another study by Mochtar, et al. also had similar conclusion that the operating time and the percentage of patients who reported tachycardia and pain were significantly higher in Novak curette group compared with the Manual Vacuum Aspiration.[10]

Discrepancy was found between the histopathological result of endometrial samples and the hysterectomy specimens. In our study, patient who had discrepancy between the histopathological result of endometrial samples and the hysterectomy specimens, underwent intraoperative frozen section and were treated with complete surgical staging.

Pathologists are dealing with increasing number of endometrial specimens in which there is scant, or even absent endometrial tissue, especially when the endometrium is atrophic. These specimens may consist entirely of superficial strips or wisps of atrophic glands, with little or no stroma, admixed with cervical mucus, ectocervical or endo-cervical tissue, and tissue from the lower uterine segment. In published studies, inadequate rates of outpatient endometrial biopsies were ranged from 4.8 to 33%; although, in most of these studies, the criteria for adequacy was not clearly mentioned.[11]

Routine criteria for adequacy of endometrial biopsies was applied by the pathologist consultant in the routine biopsy. Adequacy of the preparation was assessed as satisfactory when sufficient endometrial material (endometrial glands and stroma) was presented to make a pathological diagnosis or to exclude a pathological process. A specimen was assessed as inadequate if there was insufficient endometrial material in the cell block to exclude a pathological diagnosis. The pathologist recorded the quality of the biopsy sample and provided a diagnosis if the sample was sufficient.[9]

Our study result showed that outpatient endometrial biopsy was an accurate diagnostic procedure when adequate specimens were obtained, it had high overall accuracy in diagnosing endometrial cancer. As the diagnosis of endometrial cancer was very important, the likelihood ratio for a positive test should raise most pre-test probabilities over any threshold for advanced management. In contrast, the likelihood ratio for a negative test was not low enough to negate the need for further diagnostic testing.

Three endometrial cancers were missed among adequate biopsy specimens. Inadequate endometrial samples might come from poor biopsy technique, inherent problems with non-representative sampling, varied pathological interpretation or be consistent with the underlying atrophic endometrial state.

In our study, both inadequate samples on Pipelle were benign lesions and no case of endometrial carcinoma was missed. Our study had shown low sensitivity (76.3%) but high specificity (83.3%) for Pipelle in diagnosing benign diseases. However, malignant diseases had a sensitivity and specificity of 88.0% and 100.0%; respectively. This led to the conclusion that the Pipelle was superior for diagnosing malignant disease and hyperplasia as compared with benign diseases. This finding was reported in a study by Clark et al in 2002.[5] A finding which was also reported in a study by Festin MR, et al. in 2006, concluded that endometrial biopsy was a useful diagnostic procedure for the detection of endometrial abnormalities with accuracy of biopsy of 91.5% in patients underwent hysterectomy and was comparable to endometrial curettage with accuracy of 92.3%.[12]

CONCLUSION

The endometrial biopsy is found to be accurate, easy, and safe. However, inconsistency is found between the histopathological results of specimens obtained by endometrial sampling and hysterectomy specimens.

The disadvantages of a Pipelle biopsy are that often only very scant tissue is obtained, especially in a postmenopausal woman with an atrophic endometrium, and focal lesions may be missed. Furthermore, the frequent association between atypical hyperplasia and carcinoma means that when a diagnosis of atypical hyperplasia is made, irrespective of the sampling method, the clinician must be concerned that endometrial carcinoma exists concomitantly within the uterus.

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