Journal of the American Society of Cytopathology (2019) 8, 278–283

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jascyto.org/

ORIGINAL ARTICLE

# Role of ThinPrep liquid-based cytology in evaluation of the endocervical canal in patients with abnormal cervical screening

**Omar Al-Nourhji, MD[a], Josephine Kamtai Dermawan, MD, PhD[b], Christine N. Booth, MD[b], Dawn Underwood, MS, CT(ASCP)[b], Fadi W. Abdul-Karim, MD, MEd[b,*]**

[a] *Department of Pathology & Laboratory Medicine, College of Medicine, University of Saskatchewan, Saskatoon, Canada*
[b] *Department of Pathology, Robert J. Tomsich Pathology and Laboratory Medicine Institute, Cleveland Clinic, Cleveland, Ohio, USA*

Received 1 April 2019; received in revised form 2 May 2019; accepted 13 May 2019

**KEYWORDS**
Endocervical brushing;
Endocervical curettings;
Liquid-based cytology;
Cell blocks;
Cytohistological correlation

**Introduction** Endocervical sampling is frequently used as an adjunct to colposcopy. Few studies address the role of endocervical brushing (ECB) with liquid-based cytology (LBC) for evaluation of the endocervical canal. We assessed the roles of ThinPrep (TP) LBC of ECB specimens and cell blocks (CBs).

**Materials and methods** Pathology archives were searched for ECB specimens from 2010-2015. Preceding Papanicolaou test interpretation, human papillomavirus status, concurrent and follow-up surgical specimens, and ECB diagnoses were recorded. CB cellularity, when available, was scored on a scale of 0 to 4. The cellularity of the TP and CBs was compared.

**Results** Of 365 ECB cases, 6 (1.6%) were insufficient for diagnosis, compared with a 5% rate for endocervical curettings. Eleven ECB cases (3%) showed low cellularity. Of the 241 (66%) cases with concurrent biopsies, the ECB diagnosis agreed with the biopsy diagnosis (within 1 grade) in 198 (82%) cases. In 9 (2.5%) cases, ECB was the only means of diagnosis of a high-grade squamous intraepithelial lesion / adenocarcinoma in situ confirmed on follow-up. Compared with TP LBC, the CBs (performed in 84 [23%] of cases) were of greater cellularity in 30 (42%) and of equal cellularity in 17 (24%). None of the CBs showed an additional epithelial abnormality missed in TP LBC.

The authors declare no conflict of interest. This study was not supported by any grant or funding.

*Corresponding author: Fadi W. Abdul-Karim, MD, MEd; Department of Pathology, L25 Robert J. Tomsich Pathology and Laboratory Medicine Institute, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; Tel.: +1 216 445 3829; Fax: +1 216 445 3707.
*E-mail address:* karimf@ccf.org (F.W. Abdul-Karim).


https://doi.org/10.1016/j.jasc.2019.05.001

**Conclusions** TP LBC is capable of detecting endocervical epithelial abnormalities and may be used as a substitute for endocervical curettings. Performing a CB did not lead to detection of additional abnormalities, although it complemented TP findings and facilitates the performance of ancillary studies.


## Introduction

Colposcopy is the cornerstone for management of patients with abnormal cervical cancer screening tests. Colposcopy allows for examination of the ectocervix and surrounding vaginal wall. Nevertheless, it may not allow for adequate visualization of the transformation zone extending into the endocervical canal, especially in patients older than 40 years of age, resulting in an "unsatisfactory" colposcopic examination. Under these circumstances, or when colposcopy does not detect visible abnormalities, endocervical sampling is used as an adjunct to assess for squamous intraepithelial lesions extending into the endocervical canal.[1-8]

Despite its widespread use, patient selection for performing endocervical sampling continues to be the subject of debate.[1,2] According to the American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines,[1] endocervical sampling is generally recommended for nonpregnant patients in the setting of high-grade squamous intraepithelial lesion (HSIL) cytology, and human papillomavirus–positive atypical squamous cells of undetermined significance (ASC-US) or low-grade squamous intraepithelial lesion (LSIL), if the lesion is not fully visualized (ie, unsatisfactory colposcopy), and when there is suspicion of a glandular epithelial cell abnormality.

Sampling of the endocervical canal is conventionally performed utilizing a spoon-shaped instrument such as the Kevorkian, Sims, or Novak curettes to obtain a histologic specimen.[3] This method of sampling, designated as endocervical curettage (ECC), may be associated with minor patient discomfort,[3] false-positive and false-negative results,[4,5] and is of uncertain diagnostic utility in the setting of satisfactory colposcopic biopsies.[6-8]

Occasionally, the endocervical canal may also be assessed using a cytobrush to obtain a cytohistologic specimen.[9-20] This method, termed endocervical brushing (ECB), was reported by multiple authors to be a useful adjunct or even viable alternative to ECC.[9-19] Although most previous studies utilized conventional cytology smears,[12-16] a few studies addressed the role of liquid-based cytology (LBC) for evaluation of the endocervical canal.[18-20] The aim of our study was to assess ThinPrep (TP) LBC in

**Table 1** Interpretations of preceding Papanicolaou tests.

| Diagnosis | Number of cases (%) |
|---|---|
| High-grade squamous intraepithelial lesion (HSIL) | 39 (10.7) |
| Low-grade squamous intraepithelial lesion, cannot exclude HSIL (LSIL-H) | 16 (4.4) |
| Low-grade squamous intraepithelial lesion (LSIL) | 155 (42.5) |
| Atypical squamous cells, cannot rule out HSIL (ASC-H) | 30 (8.2) |
| Atypical cells of undetermined significance (ASC-US) | 91 (24.9) |
| Negative for intraepithelial lesion or malignancy (NILM) and positive human papillomavirus | 7 (1.9) |
| Atypical glandular cells (AGC), Not otherwise specified | 7 (1.9) |
| Atypical endocervical cells, Not otherwise specified | 6 (1.6) |
| Atypical endometrial cell, Not otherwise specified | 2 (0.5) |
| Other (post-menopausal bleeding, unsatisfactory, etc) | 7 (1.9) |
| Not identified | 5 (1.4) |
| Total | 365 |

**Table 2** Endocervical brushing cases diagnosis.

| Diagnosis | Number of cases (%) |
|---|---|
| Insufficient for diagnosis | 6 (1.6) |
| Negative | 167 (45.7) |
| Atypical cells of undetermined significance (ASC-US) | 82 (22.5) |
| Atypical squamous cells, cannot rule out HSIL (ASC-H) | 9 (2.5) |
| Low-grade squamous intraepithelial lesion (LSIL) | 68 (18.6) |
| Low-grade squamous intraepithelial lesion, cannot exclude HSIL (LSIL-H) | 4 (1.1) |
| High-grade squamous intraepithelial lesion (HSIL) | 14 (3.8) |
| Atypical cervical cells | 2 (0.5) |
| Atypical glandular cells (AGC), Not otherwise specified | 1 (0.2) |
| Atypical endocervical cells, Not otherwise specified | 7 (1.9) |
| Atypical endometrial cells, Not otherwise specified | 1 (0.2) |
| Atypical glandular cells, favor neoplastic | 1 (0.2) |
| Atypical endocervical cells, favor neoplastic | 1 (0.2) |
| Positive for malignant cells | 2 (0.5) |
| Total | 365 |

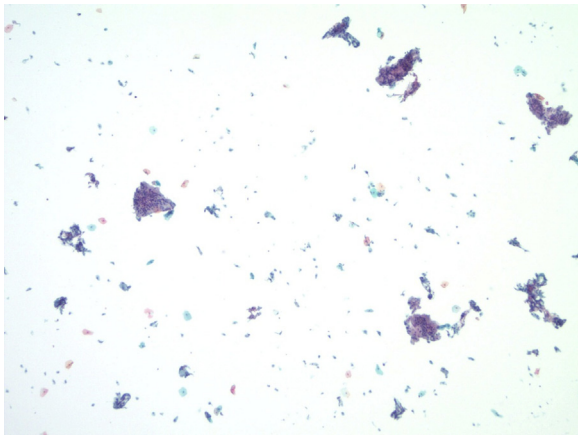

**Figure 1** Example of an ECB case showing low cellularity, but sufficient to render a diagnosis.

evaluating the endocervical canal and evaluate the role of cell blocks (CBs).

## Material and methods

Following approval of the Cleveland Clinic institutional review board, pathology archives of the Robert J. Tomsich Pathology & Laboratory Medicine Institute were searched for ECB specimens from January 2010 to December 2015. All ECB specimens were collected into CytoLyt fixative solution and processed according to the manufacturer's directions utilizing a ThinPrep processor (Hologic Inc., Marlborough, MA). Slides were stained with the Papanicolaou stain. Cellient automated CBs (Hologic Inc.) were ordered at the discretion of the signing out cytopathologist or when there were visible particles seen in the CytoLyt solution at the time of specimen preparation in the lab. All cases were signed out by a board-certified cytopathologist using The Bethesda System for Reporting Cervical Cytology.[21]

For the identified cases, patient age, the preceding Papanicolaou test interpretation, human papillomavirus status, concurrent and follow-up surgical specimens, and ECB diagnoses were recorded. CBs, when available, were reviewed and the cellularity was scored on a scale of 0 to 4 (acellular: 0; 1-10 clusters of 10 epithelial cells: 1; 11-20 clusters: 2; >20 clusters: 3; clusters containing stromal tissue: 4). The cellularity of the TP and CBs were compared.

**Table 3** Concurrent histologic sampling.

| Forms of concurrent histologic sampling (n = 272) | |
|---|---|
| Type | Number of cases (%) |
| Cervical biopsy | 241 (88.6) |
| Excisional (loop electrosurgical excisional procedure/cone) | 11 (4.0) |
| Endocervical curettage | 8 (2.9) |
| Endometrial biopsy | 11 (4.0) |
| Vaginal biopsy | 1 (0.3) |

## Results

A total of 365 ECB cases were identified. Patient age ranged from 20 to 88 years with a mean of 34 years. The majority of preceding Papanicolaou tests (Table 1) showed LSIL: 155 (42%); ASC-US: 91 (25%); HSIL: 39 (11%); low-grade squamous intraepithelial lesion, cannot exclude HSIL (LSIL-H): 16 (4%); and atypical squamous cells, cannot rule out HSIL (ASC-H): 30 (8%). In 2014, the cytopathology laboratory discontinued use of the term LSIL-H in Papanicolaou test reporting. The vast majority of LSIL-H cases are now being reported as ASC-H (unpublished data). A glandular abnormality was the preceding interpretation in 15 (4%) cases.

The diagnoses of ECB cases are listed in Table 2. On the TP preparation, 6 (1.6%) of the 365 ECB cases were insufficient for diagnosis, compared with a 5% unsatisfactory rate for ECC (no cellular material recovered on slides after processing) at our institute during the same interval (laboratory historical control) (Fig. 1).

Seventy-nine cases (22%) of the 365 ECB had no concurrent or subsequent histologic follow-up. The remaining

**Table 4** Cases with concurrent cervical biopsy.

| Cervical biopsy | Insufficient | Negative | LSIL (CIN1) | HSIL (CIN2, 3) | Squamous cell carcinoma |
|---|---|---|---|---|---|
| Endocervical brushing | | | | | |
| Insufficient | 0 | 1 | 1 | 2 | 0 |
| Negative | 2 | 33 | 56 | 12 | 0 |
| ASC-US | 1 | 16 | 32 | 17 | 0 |
| LSIL | 0 | 7 | 23 | 15 | 0 |
| LSIL-H | 0 | 0 | 1 | 1 | 0 |
| ASC-H | 0 | 0 | 1 | 4 | 0 |
| HSIL | 0 | 2 | 1 | 10 | 0 |
| AGC | 0 | 1 | 1 | 0 | 0 |
| Malignant cells present[a] | 0 | 0 | 0 | 0 | 1[a] |

[a]The squamous cell carcinoma involved the cervix extending clinically from urinary bladder primary.

**Table 5** Nine cases for which ECB was the only means of diagnosis of CIN2+/AIS confirmed on follow-up.

| ECB diagnosis | Concurrent cervical biopsy | Follow-up histologic diagnosis |
|---|---|---|
| AGC favor neoplastic | Negative | Adenocarcinoma in Situ |
| ASC-H | None | HSIL (CIN 2) |
| ASC-H | CIN1 | HSIL (CIN 2-3) |
| ASC-H | Negative | HSIL (CIN 2) |
| AGC favor neoplastic | None | Adenocarcinoma in Situ |
| HSIL | Negative | HSIL (CIN 2) |
| HSIL | CIN 1 | HSIL (CIN 2-3) |
| HSIL | CIN 1 | HSIL (CIN 2) |
| HSIL | Negative | HSIL (CIN 3)[a] |

[a]Cervical loop electrosurgical excisional procedure/cone was performed for follow-up histologic diagnosis for all cases except for this last case, which was followed-up with cervical biopsy.

286 (78%) patients had concurrent sampling and/or follow-up in the form of cervical biopsies or excisional cone. Of the 272 (75%) cases with concurrent histologic evaluation (Table 3), 241 (89%) had a concurrent cervical biopsy. The ECB and concurrent cervical biopsy diagnoses are detailed in Table 4. In these cases, the ECB diagnosis agreed with the cervical biopsy diagnosis (within 1 grade) in 198 cases (82%). In 9 (2.5%) cases, the ECB was the only means of diagnosis of HSIL (CIN 2, 3)/AIS confirmed on follow-up (Table 5).

A CB was ordered in 84 cases (23%) but was available for review in 72 cases. Cellularity of the CBs was greater than the TP LBC specimens in 30 cases (42%) and of equal quality in 17 cases (24%). The remaining 25 cases (34%) showed less cellularity, limiting the usefulness of the CBs (Tables 6 and 7). None of the CBs showed an additional epithelial cell abnormality missed in TP LBC; in fact, an epithelial cell abnormality was present in 9 cases (12.5%) in the TP LBC only (Table 7, Fig. 2). Immunohistochemical staining for p16 was utilized to establish/exclude HSIL in 3 cases with CBs in which a final diagnosis could not be reached based on cytomorphology alone.

## Discussion

Generally, after an abnormal screening Papanicolaou test and/or human papillomavirus test, women undergo colposcopy and in some cases cervical biopsy(ies) and/or ECC.[1] The addition of ECC might detect abnormalities on the endocervix that colposcopic examination may fail to sample.[2,5-8] ECC is perhaps most beneficial in detecting HSIL in women aged 40 years and older.[2,5] The performance of ECC along with random cervical biopsies, however, were also significantly associated with detection of SILs in patients with no targetable colposcopic lesions, unsatisfactory colposcopies, or lesions higher up in the endocervical canal.[6-8]

**Table 6** Cell block cellularity.

| Cellularity | Number of cases (%) |
|---|---|
| 0 | 3 (4.2) |
| 1 | 20 (27.8) |
| 2 | 7 (9.7) |
| 3 | 26 (36.1) |
| 4 | 16 (22.2) |
| Total | 72 |

ECB has been shown in previous studies to be comparable to,[9-14] if not more sensitive than, ECC.[15-19] Conventional Papanicolaou smear technique was used in the majority of previously reported studies.[12-16] On the other hand, the use of LBC in gynecologic cytology has become the mainstay in most US laboratories. It allows immediate and uniform fixation of the collected sample, reduces obscuring elements that may impact specimen interpretation, and provides the opportunity to perform molecular testing and obtain a CB if necessary. Only a few studies processed the ECB specimen using a liquid-based method.[18-20]

In a previous study by Maksem,[18] LBC ECB specimens were compared to ECC as a case-finding method. The study reported that ECB identified more cases of CIN 2 or higher compared with ECC in patients who underwent colposcopy for an LSIL or HSIL diagnosis (9.2% versus 16.8% for LSIL and 63.7% versus 72.2% for HSIL cases), and that compared with ECB, ECC was more likely to miss a diagnosis of CIN2+ (ECC versus ECB: 11.3% versus 8.1% in LSIL and 4.7% versus 1.4% in HSIL cases). Furthermore, the study found that ECB was 5 to 8 times more likely than ECC to recapitulate the highest diagnosis of the colposcopic directed biopsies (11.2% of ECC specimens detected CIN2+ in patients with CIN2+ on biopsy compared with

**Table 7** Comparison of cellularity and distribution of epithelial abnormalities between ThinPrep (TP) and cell block (CB).

| Comparison of cellularity between TP and CB | | Distribution of epithelial abnormalities between TP and CB | | |
|---|---|---|---|---|
| | Number of cases (%) | TP | CB | Number of cases (%) |
| TP > CB | 25 (34.7) | Absent | Absent | 39 (54.2) |
| TP = CB | 17 (23.6) | Present | Absent | 9 (12.5) |
| TP < CB | 30 (41.7) | Present | Present | 24 (33.3) |
| Total | 72 | Total | | 72 |

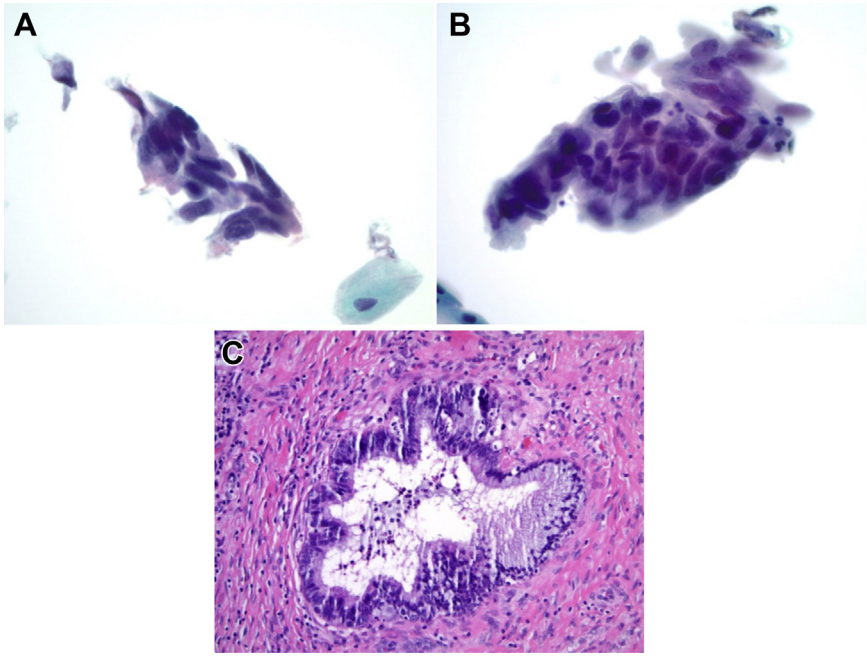


**Figure 2** (A, B) Endocervical brush ThinPrep 400X: atypical glandular cells, favor neoplasia. (C) Loop electrosurgical excisional procedure hematoxylin and eosin stain 200X: Adenocarcinoma in situ.

83.5% of the ECB specimens). The method of processing the LBC specimens was not further specified. The author concluded that LBC ECB may replace the performance of ECC during colposcopic examination.

Further support of the advantage of LBC was demonstrated in a study by Lastra et al,[19] where ECC container fluid was processed as a ThinPrep LBC specimen (CF-TP) after the surgical specimen had been drained in a mesh bag. The CF-TP diagnoses were compared to the ECC and follow-up biopsy diagnosis when available. A total of 53 specimens were examined, of which 13 (24.5%) CF-TP had a more significant diagnosis than the ECC specimen. Six CF-TP cases had a positive diagnosis confirmed on follow-up when ECC was negative. This study highlighted the potential for specimen loss during ECC processing, which can be avoided if cytology is used as the primary method for evaluating the endocervical canal.

The use of CB was not addressed in previous studies of ECB. In our cohort, CB was available for review in 72 cases. In over one third of these cases, the CBs were of greater cellularity compared with TP LBC. The performance of a CB, however, did not lead to detection of additional epithelial cell abnormalities. The potential role of p16 in CB deserves further study. In the study of conventional ECC by Shah et al,[22] a recut hematoxylin and eosin section and immunohistochemical staining with p16 were valuable adjuncts for improving the sensitivity of detection of HSIL, especially in women with a prior HSIL or ASC-H Papanicolaou test result. We used p16 in only 3 cases. However, our CB were prepared by the Cellient method, which is comparable to that of traditional paraffin-fixed CB (unpublished data).

Our study further supports the utility of ECB with TP LBC as a primary method for endocervical evaluation. In 2.5% of cases, LBC ECB was the only specimen dictating the follow-up management, which is comparable to previously reported rates.[18-20] Only 1.6% of TP LBC EBC cases contained insufficient material to establish a diagnosis, compared with a 5% unsatisfactory rate for ECC at our institution within the same time period.

## Conclusion

Cytologic-histologic correlation for cervical intraepithelial lesions or malignancies is governed by numerous clinical and pathologic factors. Colposcopy-directed biopsy is generally regarded as the "gold standard", and the role of ECC remains controversial.[23] This study demonstrates that endocervical brushing ThinPrep liquid-based cytology is capable of detecting epithelial cell abnormalities involving the endocervical canal and may be used as a substitute for endocervical curettage during colposcopy, each with its advantages and disadvantages.[9-19,23] This is concordant with previous reports comparing ECB with ECC demonstrating non-inferiority[9-14] and even higher sensitivity.[15-19] Performing a cell block did not lead to detection of additional epithelial cell abnormalities in any of the cases, although it complemented ThinPrep findings and allowed for performance of ancillary studies.

## References


1. Massad LS, Einstein MH, Huh WK, et al. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. *Obstet Gynecol*. 2013;121:829–846.
2. Diedrich JT, Felix JC, Lonky NM. Contribution of exocervical biopsy, endocervical curettage, and colposcopic grading in diagnosing high-grade cervical intraepithelial neoplasia. *J Low Genit Tract Dis*. 2016; 20:52–56.
3. Oliveira MM, Farias-Eisner RP, Pitkin RM. Endocervical sampling by Kevorkian curette or pipelle aspiration device: a randomized comparison. *Am J Obstet Gynecol*. 1995;172:1889–1892.
4. Massad LS. Selecting patients for endocervical curettage. *J Low Genit Tract Dis*. 2015;19:271–272.
5. Solomon D, Stoler M, Jeronimo J, et al. Diagnostic utility of endocervical curettage in women undergoing colposcopy for equivocal or low-grade cytologic abnormalities. *Obstet Gynecol*. 2007;110:288–295.
6. van der Marel J, Rodriguez A, del Pino M, et al. The value of endocervical curettage in addition to biopsies in women referred to colposcopy. *J Low Genit Tract Dis*. 2015;19:282–287.
7. Massad LS, Collins YC. Using history and colposcopy to select women for endocervical curettage. Results from 2,287 cases. *J Reprod Med*. 2003;48:1–6.
8. Pretorius RG, Belinson JL, Peterson P, et al. Which colposcopies should include endocervical curettage? *J Low Genit Tract Dis*. 2015; 19:278–281.
9. Goksedef BP, Api M, Kaya O, Gorgen H, Tarlaci A, Cetin A. Diagnostic accuracy of two endocervical sampling method: randomized controlled trial. *Arch Gynecol Obstet*. 2013;287:117–122.
10. Klam S, Arseneau J, Mansour N, Franco E, Ferenczy A. Comparison of endocervical curettage and endocervical brushing. *Obstet Gynecol*. 2000;96:90–94.
11. Gibson CA, Trask CE, House P, Smith SF, Foley M, Nicholas C. Endocervical sampling: a comparison of endocervical brush, endocervical curette, and combined brush with curette techniques. *J Low Genit Tract Dis*. 2001;5:1–6.
12. Weitzman GA, Korhonen MO, Reeves KO, Irwin JF, Carter TS, Kaufman RH. Endocervical brush cytology. An alternative to endocervical curettage? *J Reprod Med*. 1988;33:677–683.
13. Andersen W, Frierson H, Barber S, Tabbarah S, Taylor P, Underwood P. Sensitivity and specificity of endocervical curettage and the endocervical brush for the evaluation of the endocervical canal. *Am J Obstet Gynecol*. 1988;159:702–707.
14. Hoffman MS, Sterghos Jr S, Gordy LW, Gunasekaran S, Cavanagh D. Evaluation of the cervical canal with the endocervical brush. *Obstet Gynecol*. 1993;82:573–577.
15. Martin D, Umpierre SA, Villamarzo G, et al. Comparison of the endocervical brush and the endocervical curettage for the evaluation of the endocervical canal. *P R Health Sci J*. 1995;14:195–197.
16. Dunn TS, Stevens-Simon C, Moeller LD, Miekle S. Comparing endocervical curettage and endocervical brush at colposcopy. *J Low Genit Tract Dis*. 2000;4:76–78.
17. Mogensen ST, Bak M, Dueholm M, et al. Cytobrush and endocervical curettage in the diagnosis of dysplasia and malignancy of the uterine cervix. *Acta Obstet Gynecol Scand*. 1997;76:69–73.
18. Maksem JA. Endocervical curetting vs. endocervical brushing as case finding methods. *Diagn Cytopathol*. 2006;34:313–316.
19. Lastra RR, Meykler SE, Baloch ZW, Barroeta JE. Increasing the sensitivity of endocervical curettings by performing ThinPrep® Pap on transport container fluid: is diagnostic material going down the drain? *Cytopathology*. 2015;26:368–372.
20. Kim HS, Park JS, Park JY, et al. Comparison of two preparation methods for endocervical evaluation. *Acta Cytol*. 2007;51:742–748.
21. Solomon D, Nayar R. *The Bethesda System for Reporting Cervical Cytology: Definitions, Criteria, and Explanatory Notes*. 3rd ed. New York: Springer; 2015.
22. Shah AA, Jeffus SK, Zhao Z, Stoler MH, Stelow EB. Adjunct p16INK4a immunohistochemistry aids the detection of high-grade squamous intraepithelial lesions in endocervical curettage specimens. *Am J Clin Pathol*. 2014;141:342–347.
23. Abdul-Karim FW, Yang B. Cytologic-hstologic discrepancies in pathology of the uterine cervix: analysis of the clinical and pathologic factors. *Adv Anat Pathol*. 2017;24:304–309.