# Cytology at the time of cervical colposcopy

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**Summary**

*Objective:* The efforts of the authors are to evaluate the role of performing a Papanicolaou (Pap) smear at the time of colposcopy. *Materials and Methods:* This retrospective chart review included patients from 2004 to 2009 who underwent cold knife cone (CKC) biopsy or loop electrosurgical excision procedure (LEEP) for cervical intraepithelial neoplasia types 2 and 3 (CIN 2 and 3) or patients with discrepancy between Pap and colposcopic results. All patients presented to the gynecology clinics in a tertiary care hospital. Results were compared which included: the abnormal Pap smear which led to referral for colposcopy, the Pap smear performed at the time of colposcopy, the colposcopic biopsy, and the excisional biopsy. Interpretation of results was calculated with Cohen's κ Statistics. *Results:* One hundred forty-seven patients qualified for the study. One hundred five patients had excisional biopsy proven high-grade squamous intraepithelial lesion (HSIL). Eighty-two of these high-grade excisional pathology results were preceded by high-grade Pap cytology at the time of colposcopy; however 23 Pap cytology results indicated either low-grade squamous intraepithelial lesion (LSIL) or negative (20 and 3 respectively), but were followed by an excisional procedure revealing high-grade pathology. Eighty-one colposcopic biopsies confirmed high-grade excisional biopsy pathology. However, 24 colposcopic biopsies were low-grade or negative (13 and 11 respectively), but followed by a high-grade excisional biopsy. *Conclusion:* The addition of a Pap smear at the time of colposcopy has the potential role of recognizing high-grade cervical dysplasia.

*Key words:* Colposcopy; Papanicolaou (Pap) smear; High-grade squamous; Intraepithelial lesion (HSIL).

## Introduction

Since the 1950s, the steady decline in cervical cancer incidence and mortality has been attributed to widespread cervical cancer screening [1, 2]. The Papanicolaou (Pap) smear is the most commonly utilized method to detect these lesions; however occasionally results are reported as normal when abnormal cells are present (false negative). Additionally, results are sometimes reported as abnormal when there are only normal cells (false positive). Over 90% of Pap smears will be diagnosed "negative for intraepithelial lesion or malignancy" [3].

Other cytology results from Pap smears are stratified by severity, and can include: low-grade squamous intraepithelial lesions (LSIL) and high-grade squamous intraepithelial lesions (HSIL), amongst others. Histology results are likewise classified as CIN 1, 2, and 3. CIN 1 is the most benign and considered a manifestation of infection with human papillomavirus (HPV). CIN 2 and 3 are progressively more severe precursors of cervical cancer [4]. HSIL cytology is consistent with a diagnosis of CIN 2 or 3 and can include: hyperchromatic nuclei, abnormal chromatin distribution, nuclear atypia or pleomorphism, and increased nuclear/ cytoplasmic ratio. Milder manifestations of these changes achieve a diagnosis of LSIL cytology or CIN I histology [5].

A large proportion of LSIL (61%) is destined to spontaneously regress in 12 months, especially in adolescents [6]. However, CIN 2 or 3 has a regression of only 35% [7]. HSIL patients are almost always managed with colposcopy and biopsy as a first step. However, colposcopy following HSIL cytology can miss a significant number of CIN 2 and 3 lesions. Therefore most women with HSIL eventually undergo an excisional procedure [8]. This procedure includes either the loop electrosurgical excision procedure (LEEP) or cold knife conization (CKC). LEEP consists of removing the transformation zone or squamocolumnar junction and can be performed under local anesthesia in an office setting [9]. CKC can be utilized to obtain endocervical tissue and it is achieved with a scalpel incision of the cervix under general anesthesia.

It is important to have an accurate diagnosis of cervical dysplasia as excisional procedures have associated risks greater than Pap and colposcopy. All excisional procedures including LEEP and CKC may predispose to low birth weight and preterm birth [10-12]. Whether this is truly causal and not simply an association remains unclear [13]. For example, risks of cervical dysplasia and preterm delivery each include smoking, low socio-economic status, and infection [14]. Jakobsson *et al*. found that surgery itself and not the background characteristics explain the increased risk for preterm birth [14]. Therefore, there is a need for an intermediate tool in the management of cervical dysplasia to increase the sensitivity of the recognizing high-grade dysplasia.

In this study, the authors' objective was to examine the value of Pap smear at the time of colposcopy as noninvasive means to improve the accuracy of the diagnosis of cervical dysplasia. This retrospective chart review compares both Pap at the time of colposcopy and the colposcopic exam alone to the final pathology of the excisional procedure.

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## Materials and Methods

A retrospective chart review was performed and included patients undergoing LEEP or CKC for CIN 2 and 3 or discrepancy between Pap and colposcopy from January 1st, 2004 to December 31st, 2009.

Data was obtained from medical charts (pathology reports) and included the results of the last (most recent) abnormal Pap smear which led to referral for a colposcopic exam, results of the Pap smear performed at the time of colposcopy, colposcopic biopsy results, and the results of the excisional biopsy.

Women who had colposcopy performed followed by successive cone biopsy or LEEP were included in this study. Colposcopy was performed on patients with HSIL on Pap smear cytology, persistent LSIL, atypical squamous cells (ASC), or atypical glandular cells (AGC). Patients with cervical cancer were excluded due to the small number of cases to avoid statistical inconvenience, and patients with inconclusive biopsy results unable to be classified were also excluded. All colposcopic exams were performed and documented the same way; the key concepts of the system included: aceto-white reaction, color, margins, and vessels examined to formulate a colposcopic impression and to aid in the selection of the most appropriate sites for colposcopically-directed biopsy. Three percent acetic acid solution was applied to the surface to improve visualization of abnormal areas. Monsel's solution was applied with large cotton swabs to the surface of the cervix to achieve hemostasis.

Liquid-based technology Thin Prep, was utilized for all Pap smears in the present study. Cervical cells were transferred to the specimen vial with a broom-like device and immersed into liquid fixative, fixing the cells instantly.

In this study, the guidelines implemented were in accordance with the 2001 American Society for Colposcopy and Cervical Pathology and updated 2001 Bethesda classification.

The summaries on the measurement results (HSIL, LSIL, and normal) are displayed in frequency tables and Kappa coefficients are estimated to assess agreement between two measurement methods as any pair of the three methods: excisional biopsy, colposcopic biopsy, and Pap smear performed at the time of colposcopy. For most purposes, Kappa coefficients greater than 0.75 may be taken to represent excellent agreement, below 0.40 may be interpreted as poor agreement, and between 0.40 and 0.75 may be understood as intermediate agreement recommended by Landis and Koch [15].

## Results

Institutional review board approval was obtained to review medical records for 147 patients who underwent an excisional procedure for cervical dysplasia. Of this total, 105 patients revealed high-grade pathology. Among these 105 patients, 82 cases were further diagnosed with Pap smear at the time of colposcopy and colposcopy as compared to 81 cases of high-grade dysplasia by colposcopic biopsy (Tables 1 and 2). Twenty-three Pap smears at the time of colposcopy were read as low-grade dysplasia or negative for dysplasia and were followed by a high-grade excisional biopsy (LSIL 20 cases and negative in three cases). Similarly 24 (LSIL 13 cases and negative in 11 cases) colposcopic biopsies were low-grade or negative for dysplasia, but preceded an excisional biopsy of high-grade dysplasia.

One hundred seven Pap results were HSIL. Of this group, six were low-grade and 19 were negative for dysplasia from the excisional pathology report. Ninety-nine colposcopic biopsies were high-grade dysplasia. Of this group, five were low-grade and 13 were negative for dysplasia from the excisional pathology evaluation.

The Pap smear and colposcopic biopsy together compared to excisional biopsy pathology is presented in Table 3.

Table 1. — *Cervical cytology at the time of colposcopy compared to subsequent excisional biopsy pathology*.

| Pap smear at colposcopy | Excision biopsy HSIL | LSIL | Negative | Total |
|---|---|---|---|---|
| HSIL | 82 | 6 | 19 | 107 |
| LSIL | 20 | 5 | 11 | 36 |
| Negative | 3 | 1 | 0 | 4 |
| Total | 105 | 12 | 30 | 147 |

HSIL = high-grade squamous intraepithelial lesion (CIN2-CIN3).
LSIL = low-grade squamous intraepithelial lesion (CIN1-HPV changes).

Table 2. — *Colposcopic biopsy compared to subsequent excisional biopsy pathology*.

| Colposcopy | Excision biopsy HSIL | LSIL | Negative | Total |
|---|---|---|---|---|
| HSIL | 81 | 5 | 13 | 99 |
| LSIL | 13 | 5 | 9 | 27 |
| Negative | 11 | 2 | 8 | 21 |
| Total | 105 | 12 | 30 | 147 |

Table 3. — *Pap smear and colposcopy together compared to excisional biopsy pathology*.

| PAP/Colposcopy | Excision biopsy HSIL | LSIL | Total |
|---|---|---|---|
| H/H | 63 | 12 | 75 |
| | 84.00 | 16.00 | |
| | 60.00 | 28.57 | |
| H/L | 19 | 13 | 32 |
| | 59.38 | 40.63 | |
| | 18.10 | 30.95 | |
| L/H | 18 | 6 | 24 |
| | 75.00 | 25.00 | |
| | 17.14 | 14.29 | |
| L/L | 5 | 11 | 16 |
| | 31.25 | 68.75 | |
| | 4.76 | 26.19 | |
| Total | 105 | 42 | 147 |

H = HSIL; L = LSIL.

## Discussion

In the ASCUS-LSIL Triage Study (ALTS), the sensitivity of initial colposcopy for CIN3 identified during two years of observation was only 54% [16].

In the present study, Pap at the time of colposcopy and colposcopic exam had similar ratios (82 vs 81 cases) of making the diagnosis of high-grade dysplasia. Among the cases with high-grade excisional pathology, there were only three patients with false-negative results (2.8%). However this number was 11 cases (10.4%) for colposcopy. Therefore, Pap smear may have a lower false-

negative rate in comparison to colposcopy in the recognition of high-grade cervical dysplasia.

The two approaches: Pap at the time of colposcopy and colposcopy alone agreed on high-grade diagnosis for only 63 patients. Individually, 18 high-grade excisional biopsies were previously correctly diagnosed as high-grade by colposcopy with an incorrect "benign" Pap smear report. Nineteen high-grade excisional biopsies correlated with high-grade Pap reports with an incorrect low-grade colposcopic diagnosis. When these two techniques are utilized together, a total of 100 patients (95.2%) would be accurately diagnosed with high-grade cervical dysplasia.

Literature reveals the positive predictive value (PPV) of agreement of high-grade colposcopic impression with high-grade histology ranges from 39% to 70% [17, 18]. The false-positive rate of Pap smear and colposcopy to incorrectly diagnose high-grade dysplasia instead of low-grade or negative dysplasia in this study was 23.3% and 18.1%, respectively. Certainly inter-observer variability or spontaneous regression of the lesion may play a role. Possibly, the decrease in false-positives from colposcopy can be attributed to complete treatment of a small cervical lesion during the colposcopic biopsy.

In practice, the present clinicians perform a Pap smear at the time of colposcopy for patients that are referred to the Institution because the previous Pap is usually obtained from another institution and reviewed by pathologists outside this Institution. Additionally, there is an approximate delay of 88 to 124 days between Pap smear at the referring clinic and colposcopy at this Institution. The authors' efforts are focused on catching the possibility of spontaneous regression during this time and making the accurate diagnosis to increase the quality of care for the patients.

For physicians who do not routinely perform a Pap smear at the time of colposcopy, the additional Pap smear will increase care costs slightly. However, concurrent use of colposcopy and Pap smear increases the accurate diagnosis of high-grade cervical dysplasia, which may otherwise be missed by following the current guideline algorithms.

## References

[1] Cancer Facts & Figures 2011. Available at the American Cancer Society Website: http://www.cancer.org/Research/CancerFactsFigures/CancerFactsFigures/cancerfacts-figures-2011. Accessed August 22, 2011.

[2] Waxman A.G., Zsemkye M.M.: "Preventing cervical cancer: the Pap test and the HPV vaccine". *Med. Clin. North. Am.,* 2008, *92,* 1059.

[3] Joste N.: "Overview of the cytology laboratory: specimen processing through diagnosis". *Obstet. Gynecol. Clin. North Am.,* 2008, *35*, 549.

[4] Sawaya G.: "Cervical cancer screening - new guidelines and the balance between benefits and harms". *N. Engl. J. Med.,* 2009, *361,* 2503.

[5] Zsemlye M.: "High-grade cervical dysplasia: pathophysiology, diagnosis, and treatment". *Obstet. Gynecol. Clin. North Am.,* 2008, *35*, 615.

[6] Moscicki A.B., Shiboski S., Hills N.K., Powell K.J., Jay N., Hanson E.N. *et al.*: "Regression of low-grade squamous intraepithelial lesions in young women". *Lancet,* 2004, *364,* 1678.

[7] Melnikow J., Nuovo J., Willan A.R., Chan B.K., Howell L.P.: "Natural history of cervical squamous intra-epithelial lesions: a meta-analysis". *Obstet. Gynecol.,* 1998, *92,* 727.

[8] Wright T.C. Jr., Massad L.S., Dunton C.J., Spitzer M., Wilkinson E.J., Solomon D.; 2006 American Society for Colposcopy and Cervical Pathology-sponsored Consensus Conference: "2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests". *Am. J. Obstet. Gynecol.,* 2007, *197,* 346.

[9] Katz V.L., Lentz G.M., Lobo R.A., Gershenson D.M. (eds.). Comprehensive Gynecology, 5th ed., Chap 28; Intraepithelial Neoplasia of the Lower Genital Tract - Excisional Methods, Philadelphia, Pa: Mosby Elsevier, 2007.

[10] Arbyn M., Kyrgiou M., Simoens C., Raifu A.O., Koliopoulos G., Martin-Hisch P. *et al.*: "Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: meta-analysis". *BMJ,* 2008, *337,* 1284.

[11] Kyrgiou M., Koliopoulos G., Martin-Hirsch P., Arbyn M., Prendiville W., Paraskevaidis E.: "Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis". *Lancet,* 2006, *367,* 489.

[12] Jakobsson M., Gissler M., Sainio S., Paavonen J., Tapper A.M.: "Preterm delivery after surgical treatment for cervical intraepithelial neoplasia". *Obstet. Gynecol.,* 2007, *109,* 309.

[13] Jakobsson M., Bruinsma F.: "Adverse pregnancy outcomes after treatment for cervical intraepithelial neoplasia". *BMJ,* 2008, *337,* 1350.

[14] Jakobsson M., Gissler M., Paavonen J., Tapper A.M.: "Loop electrosurgical excision procedure and the risk for preterm birth". *Obstet. Gynecol.*, 2009, *114,* 504.

[15] Fleiss J.L.: "Statistical methods for rates and proportions". Second ed., New York, John Wiley, ISBN 0471263702, 1981.

[16] ASCUS-LSIL Traige Study (ALTS) Group: "Results of a randomized study on the management of cytology interpretation of atypical squamous cells of undetermined significance". *Am. J. Obstet. Gynecol.,* 2003, *188,* 1383.

[17] Trivers K.F., Benard V.B., Eheman C.R., Royalty J.E, Ekwueme D.U., Lawson H.W.: "Repeat pap testing and colposcopic biopsies in the underserved". *Obstet. Gynecol.*, 2009, *114,* 1049.

[18] Massad L.S., Collins Y.C.: "Strength of correlations between colposcopic impression and biopsy histology". *Gynecol. Oncol.,* 2003, *89,* 424.

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