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### Evidence-Based Medicine Two-Step Discrepancy

In 2006 the American Society for Colposcopy and Cervical Pathology (ASCCP) released its most recent guidelines (Wright Jr. et al., 2007). These guidelines represent a consensus of about management of women who have abnormal pap smears and the management of these abnormalities. The ASCCP jointed with professional groups, federal and international organizations, and experts in cervical cancer prevention to improve the care of women with CIN by weighing the best available evidence and develop consensus on management (Wright Jr. et al.) Due to the appropriate evaluation and management of Cervical Intraepithelial Neoplasia (CIN) in recent years, rates of cervical cancer have continued to decline in recent years.

When results of colposcopy are evaluated to make recommendations regarding treatment it is important that the results of the referring Pap smear, colposcopic impression, as well as biopsy results be correlated. Discrepancies between the referring cervical cytological findings and the subsequent histological findings are common and need to be considered when making treatment decisions for CIN (Lanneau et al., 2007, p. 133) In cases where the cervical cytological finding is high-grade squamous intraepithelial lesion (HSIL) and the histological results are normal or CIN 1 (mild dysplasia) an excisional procedure is necessary for treatment (Lanneau et al., p. 133). This is commonly called a two-step discrepancy.

In 2001 the Bethesda Terminology guidelines were released to give consensus to the laboratory reporting guidelines to the results of cervical cytology results. High-grade squamous intraepithelial lesion (HSIL) lesions can be classified as moderate to severe dysplasia or high grade squamous intraepithelial lesion encompassing moderate, severe dysplasia, and CIS (carcinoma in situ) (Apgar, Gregory, & Mark, 2002, p. 250).

### Purpose of this Project

The purpose of this project is to pose the question in a patient who presents with a High-Grade Pap (encompassing CIN2/CIN3 and CIS) and a biopsy reporting CIN2 (and is otherwise a good candidate for cryosurgery) is cryosurgery adequate treatment for this patient or is this an example of a two-step discrepancy and the patient needs to have an excisional procedure (leep/conization). This is an important question to reconcile for optimal effectiveness of treatment as well as medical legal reasons.

This clarification is important because discrepancies occur frequently within results and a clear understanding of what is and is not considered a discrepancy is important. Discrepancies can occur for a variety of reasons including an overcall of cytological findings or a sampling error during colposcopy (when area of dysplasia is missed on biopsy) (Lanneau, 2007). In cases where the cytological (Pap) result is HSIL and histological (biopsy) is normal or low grade (CIN1) an excisional procedure is recommended (Lanneau, 2007). This recommended procedure is to find the high-grade lesion presumably missed on colposcopy and includes the endocervix as well (Lanneau, 2007). The purpose of this question is to discover if the finding of CIS (Carcinoma in Situ) is being missed when the biopsy is confirmed as being moderate dysplasia and needs an excisional procedure or if CIS is treated the same way as CIN3 and cryosurgery is an adequate treatment.

### Methodology

The methodology that was used during this search of the literature was obtained from a search of current findings through the nursing databases and through a literature search through SCOPUS. After searching through SCOPUS, I also reviewed articles that were related to the ASCCP guidelines for treatment and management of cervical intraepithelial neoplasia that were

released in 1998 as well as 2006. I also reviewed the results of the Bethesda Terminology and Evidence-Based Management Guidelines for Cervical Cytology Findings. I also contacted a coworker who belongs to the ASCCP and have access to the last 30 issues of the Journal of Lower Genital Tract Disease published by the ASCCP. The journal articles that were in the preceding journal were the most helpful because they were published for the specialty topic of research. Multiple articles were also obtained after accessing the reference lists on both the ASCCP guidelines for both cytology and histologic findings that were published in 2007. Cochrane Database for Systematic Reviews released systematic review of surgical procedures to treat cervical intraepithelial neoplasia in 1999, which was updated in 2004 and was unchanged as of July 26, 2009.

#### Definition of Terms

For the purposes of this project, the following terms were defined: ASCCP, CIN1, CIN2, CIN3, CIS, cervical dysplasia, colposcopy, conization, cryosurgery, LEEP, ablation, and two-step discrepancy, as well as LSIL and HSIL.

The ASCCP is an acronym for The American Society of Colposcopy and Cervical Pathology. Cervical intraepithelial neoplasia (CIN), previously dysplasia, means disordered growth and development of the epithelial lining of the cervix (Holschneider, 2007, p. 1). Furthermore, there are various degrees of this disordered growth as dependent on the amount of epithelial lining of the cervix is involved: CIN 1 (mild dysplasia) encompasses the lower one third of the epithelial thickness, CIN 2 (moderate dysplasia) encompasses the lower two-thirds of the epithelium, and CIN 3 (severe dysplasia) involves more than two-thirds of the epithelium. Carcinoma In Situ (CIS) involves the full thickness of the cervical epithelium. According to this

reference, Low-grade squamous intraepithelial lesion describes CIN 1. High-grade squamous intraepithelial lesion is listed as CIN 2, CIN3, and CIS.

Colposcopy is the primary technique for visualization and evaluation of the cervix after receiving abnormal cytology results. According to Holschneider (2007, p. 4), the colposcope is an instrument that uses low-power magnification to inspect the cervix, vagina, vulva, or anal epithelium. She further states that abnormalities in the epithelium can be visualized after application of acetic acid and biopsies of the abnormal epithelium are taken and processed in the lab by a pathologist to evaluate these abnormalities. Conization of the cervix is when a cone shaped section (including a portion of the endocervical canal) is removed and sent to pathology to evaluate the cervix in special situations, such as dysplasia on the endocervical curettage (ECC), significant discrepancy between cytology and histology, if adenocarcinoma in situ or if microinvasive carcinoma is suspected (Holschneider, 2007, p. 5).

Several treatment options (described below) are available for treatment such as ablation-laser and cryotherapy as well as two excisional procedures-conization and LEEP (Holschneider, 2007, p. 6). Cryotherapy or cryosurgery is an in office procedure where the surface of the cervix is frozen with nitrous oxide using 2 separate freezes to a depth of 5-7 mm which does not require anesthesia and can be done in an office setting. Laser surgery is a procedure that requires anesthesia and works to also remove the abnormalities by destroying the tissue. LEEP is an in office procedure that is done under a local anesthesia that removes the abnormal cervical tissue with a wire loop in an office or surgical setting. Conization also requires anesthesia in a surgical setting and is used for more extensive abnormalities. A two-step discrepancy is when there is a lack of correlation between the findings of cervical cytology (HSIL) and normal histology on biopsy with satisfactory colposcopic examination (Lanneau et al., 2007, p. 134).

LSIL or low grade squamous intraepithelial lesions are considered to be indicative of persistent infection by the human papilloma virus (HPV) which results in the growth of epithelial cells which are flat and papillary in nature (O'Connor, 2008, p. 569). This type of lesion is considered to be a much more benign lesion than HSIL and will usually regress about 80% of the time without treatment (Saslow et al., 2003, p. 69).

HSIL or high-grade squamous intraepithelial lesion is a term that describes the categories of CIN 2,3 as expressed by the ASCCP (Wright Jr. et al., 2007, p. 230). CIN 2,3 share many characteristics that are precursors to cervical cancer, and are therefore, the threshold for treatment except in special situations (pregnancy, and the teen population) (Wright Jr. et al., 2007, p. 230). These categories are defined in this regard because of the increased risk of progression to cervical cancer if untreated and therefore are considered high grade.

One further description of the terminology for this project is indicated. According to Zsemlye (2008), the designation of CIN 2,3 includes lesions formally referred to as moderate dysplasia (CIN 2), severe dysplasia (CIN 3), or carcinoma in situ (CIS (CIN3)).

Discussion of the terminology that describes characteristics of cellular characteristics found in abnormal cytologic and histologic specimens can be confusing and not necessarily straightforward. Cervical cancer precursors were presented in the following table used to describe findings between the Bethesda System, International Society of Gynecologic

Pathologists and the World Health Organization (Soto-Wright, Samuelson, & McLellan, 2005, p.

Terminology for Cervical Cancer Precursors

Squamous Intraepithelial Lesion (SIL)				
Low Grade			High Grade	
Condyloma	Cervical Intraepithelial Neoplasia (CIN)			
	Grade 1	Grade 2	Grade 3	
Normal	Very Mild-Mild Dysplasia	Moderate Dysplasia	Severe Dysplasia	In situ Carcinoma

148). A copy of the table is shown below:

### Literature Review

Cochrane database of systematic reviews published a systematic review of surgery for cervical intraepithelial neoplasia first in 1999, reviewed in 2004, and again reviewed in 2009 (Martin-Hirsch, Paraskevaidis, & Kitchener, 1999). According to the review, twenty eight trials were included in the review of seven surgical techniques. Large loop excision of the transformation zone provided the most correlation between histology with the least morbidity (Martin-Hirsch et al., p. 1). In this review the authors' conclude that there is no obviously superior surgical technique for treating cervical-intraepithelial neoplasia (Martin-Hirsch et al., p. 1). According to this review, patients are suitable candidates for ablative therapy if the entire transformation zone can be visualized (have satisfactory colposcopy), there is no suggestion of microinvasive or invasive disease, no suspicion of glandular disease, and the cytology and histology correspond (Martin-Hirsch et al., p. 2).

At the time of the original systematic review most of the studies on cryotherapy were non-controlled studies which showed varied effectiveness of the treatment of CIN3 from 77% to 93% (Martin-Hirsch et al., p. 2). Many of the randomized clinical trials done on cryosurgery that were reviewed (5 of the 6) were based on single freeze technique and one on double freeze

technique (Martin-Hirsch et al., p. 3). When reviewed, these results were lower than acceptable for standard of treatment unless double freeze techniques were used (Martin-Hirsch et al., p. 3). According to this review cryosurgery is not recommended for high grade disease, but only recommended only for the treatment of mild disease (Martin-Hirsch et al., p. 7). Double freeze technique with cryosurgery is now the standard of care and single freeze techniques are no longer used. This review was done prior to the ASCCP consensus guidelines that were released in 2006 and is not considered to be as valid as the consensus guidelines.

UpToDate online search was also accessed to compare opinions regarding current treatment for CIN 2,3 using cryotherapy. They recommend cryotherapy not be used in women with CIN 2,3 because the overall cure rate of cryosurgery was 88.3% when compared to 96.4% cure rate found in LEEP in a randomized controlled trial done in 2001 (Chirenje, Rusakaniko, Akino, & Mlingo, 2001, p. 620). During this trial discussed above, a double-freeze technique was used to treat the women during cryosurgery.

According to Burghardt, Pickel, & Girardi (1998) only specific criteria exist for the performance of ablative modalities: the lesion is limited to CIN 1 or CIN 2, the lesion is small and smooth, and purely on the ectocervix, and the entire squamocolumnar junction is visible. If all of these criteria can't be met then ablation is not a satisfactory treatment option.

According to Apgar, Brotzman, & Spitzer (2002) cryosurgery should be advocated when the lesion is smaller than two quadrants of the cervix, the cervix needs to be smaller than 3-3.5 cm in diameter, and the lesion must not include the endocervix. All of these criteria must be met prior to cryotherapy, and the above authors also suggest that CIN 3 not be treated by cryosurgery but excisional methods instead.



The 2001 Bethesda System was revised by a group of more than 400 participants including pathologists, cytotechnologists, clinicians, and patient advocates as well as more than forty-four workshop cosponsors (Solomon, Davey, & Kurman, 2002, p. 2115). Within these guidelines, it is important to remember that some of the recommendations are based on randomized clinical trials, small descriptive studies, or in cases where information was limited on expert opinion (Wright Jr. et al., 2007, p. 225)

According to the ASCCP guidelines, cryosurgery continues to be adequate treatment for initial treatment of CIN2/CIN3 of the cervix (Wright Jr. et al., 2007). To be an effective treatment for CIN 2,3 the focus of treatment needs to remove the entire transformation zone, rather than focus on the lesion identified by colposcopy (Wright Jr. et al., p. 230). Clinical trials comparing ablative and excisional treatments in the treatment of biopsy confirmed CIN 2,3 and satisfactory colposcopy have not shown significant differences in outcomes (Wright Jr. et al., p. 231). If a woman has a large lesion, the lesion extends into the cervical os (opening), or this is a recurrence of CIN 2,3 she is no longer a candidate for ablation and needs an excisional procedure (Wright Jr. et al., p. 231). In patients who had ablative therapy and subsequently developed invasive cervical cancer following treatment of CIN or HPV were found to be inappropriate candidates for cryotherapy (large lesion, positive ECC, or unsatisfactory colposcopy) and cryotherapy was done despite this fact (Schmidt et al., 1992).

There are several important considerations to evaluate in a woman with HSIL on a Pap smear. It also should be considered that failure to biopsy CIN 2 or CIN 3 at colposcopy does not mean that a CIN 2 or CIN 3 lesion is not present, although occult carcinoma is unlikely (Wright Jr. et al., 2007, p. 209). Conization of the cervix was primarily thought to have more risk of leading to prematurity, and cervical incompetence, but recently findings suggest that LEEP

seems to approximately double the risk for a woman to have preterm delivery, preterm rupture of membranes, or a low-birth weight infant so this needs to be considered when making recommendations for treatment (Wright Jr. et al., p. 210).

Several studies have demonstrated the strong correlation between a HSIL cytology result and biopsy findings of CIN 2/CIN3. According to Numnum et al. (2005) who did a see-and-treat study of HSIL that 84% of treated patients also had CIN 2/3 identified on the LEEP specimen. Of the individuals admitted into this study, none of the individuals were excluded from the study for a lesion that was suspicious for invasive cervical cancer, and none of the LEEP histology specimens showed invasive carcinoma (Numnum et al., 2005, p. 4). Dunn (2003), however, reports a correlation of 94% of HSIL cytological results that were treated also had CIN 2/CIN 3 on histological results from LEEP, and 3 of the individuals who were treated also had findings of microinvasive cancer. Dunn et al. (2003) also admitted individuals into the see-and-treat strategy that would not be good candidates for ablative therapy and at higher risk for cervical cancer (those with unsatisfactory colposcopy). This correlation is important when considering ablation for HSIL cytological results as well as CIN 2 histology findings because it helps to assure that treatment by ablation is not done in those with more abnormal histologic findings (invasive carcinoma).

Adding to the complexity of this issue is the status of the endocervix. If the lesion found on colposcopy is not completely visualized this is an unsatisfactory colposcopy and the patient is not a candidate for cryosurgery. If the colposcopy is satisfactory and the lesion does not appear to extend into the endocervix, endocervical curettage or ECC is performed along with ectocervical biopsies during the colposcopy procedure. It is generally accepted that a HSIL pap needs to be evaluated with the minimum of an ECC and colposcopically guided biopsies unless

the patient is pregnant. If the biopsy results show an abnormal ECC, excisional treatment must be undertaken (Wright Jr. et al., 2007). To further complicate the issue, ECC results have been shown to have a false positive rate in satisfactory colposcopy (Zsemlye, 2008, p. 617). In a 2004 study of endocervical curettage done during colposcopy was found to be positive approximately 6.4 % of the time and changed the type of treatment that was received during that study (Zsemlye, p. 617).

### Conclusion

According to Current Diagnosis & Treatment Obstetrics & Gynecology (Holschneider, 2007), CIN 3 or severe dysplasia encompasses more than two-thirds of the epithelium and CIS or carcinoma in situ represents the full-thickness or three-thirds of the epithelium (Holschneider, p. 1). Both excision and ablation are acceptable treatment strategies with histological diagnosis of CIN 2,3 in primary treatment (Wright Jr. et al., p. 231). According to the ASCCP CIN2/CIN3/CIS is considered to be all within the same category of HSIL and therefore treated within the same guidelines (Wright Jr. et al., p. 209). Therefore, the ASCCP consider CIN3/CIS to be interchangeable and guidelines to be sufficient in management of these abnormalities. Therefore this is not considered to be a two-step discrepancy within the guidelines discussed by the ASCCP and cryosurgery is an acceptable treatment for CIN 2,3 on the surface of the cervix with satisfactory colposcopy. During this evaluation of the evidence of this project clear answers were not readily available in the literature. At this current time I have presented this question to the director of dysplasia services at Parkland here in Dallas to have another opinion regarding this question, but have not received an answer as of yet.

## References

- Apgar, B. S., Gregory, B. L., & Mark, S. (2002). *Colposcopy, Principles and Practice: An Integrated Textbook and Atlas*. Philadelphia, PA: W.B. Saunders Company.
- Burghardt, E., Pickel, H., & Girardi, F. (1998). *Colposcopy Cervical Pathology Textbook and Atlas* (3rd ed.). New York: Thieme Stuttgart.
- Chirenje, Z. M., Rusakaniko, S., Akino, V., & Mlingo, M. (2001). A randomized clinical trial of loop electrosurgical excision procedure (LEEP) versus cryotherapy in the treatment of cervical intraepithelial neoplasia. *Journal of Obstetrics and Gynaecology*, *21*, 617-621.
- Dunn, T. S., Burke, M., & Shwayder, J. A. (2003). "See and treat" management for high-grade squamous intraepithelial lesion pap smears. *Journal of Lower Genital Tract Disease*, *7*, 104-106.
- Holschneider, C. H. (2007). Premalignant & Malignant Disorders of the Uterine Cervix. In A. H. DeCherney, L. Nathan, T. M. Goodwin, & N. Leufer (Eds.), *Current Diagnosis & Treatment Obstetrics & Gynecology* (pp. 1-24). New York: Lange Medical Books/McGraw-Hill Medical Publishing Division.
- Lanneau, G. S., Skaggs, V., Moore, K., Stowell, S., Zuna, R., & Gold, M. A. (2007). A LEEP cervical conization is rarely indicated for a two-step discrepancy. *American Society for Colposcopy and Cervical Pathology Journal of Lower Genital Tract Disease*, 134.
- Martin-Hirsch, P., Paraskevaïdis, E., & Kitchener, H. C. (1999). Surgery for cervical intraepithelial neoplasia. *Cochrane Database of Systematic Reviews*, (3), 1-60.
- Numnum, T. M., Kirby, T. O., Leath, C. A., 3rd, Huh, W. K., Alvarez, R. D., & Straughn, J. M., Jr. (2005). A prospective evaluation of "see and treat" in women with HSIL Pap smear results: Is this an appropriate strategy?. *Journal of Lower Genital Tract Disease*, (9), 2-6.

- O'Connor, D. M. (2008). A tissue basis for colposcopic findings. In (Series Ed.) & (Vol. Ed.), :  
Vol. . ( ed., pp. -p. ). : .
- Saslow, D., Runowicz, C. D., Solomon, D., Moscicki, A. B., Smith, R. A., & Eyre, H. J. et al.  
(2003). American Cancer Society guideline for early detection of cervical neoplasia and  
cancer. *Journal of Lower Genital Tract Disease*, 7(2), 67-86.
- Schmidt, C., Pretorius, R. G., Bonin, M., Hanson, L., Semrad, N., & Watring, W. (1992).  
Invasive cervical cancer following cryotherapy for cervical intraepithelial neoplasia or  
human papillomavirus infection. *Gynecologic Oncology*, 71(71), 46-49.
- Solomon, D., Davey, D., & Kurman, R. (2002). The 2001 Bethesda System: Terminology for  
reporting results of cervical cytology. *JAMA*, 287, 2114-2119.
- Soto-Wright, V., Samuelson, R., & McLellan, R. (2005). . *Current management of low-grade  
squamous intraepithelial lesion, high-grade squamous intraepithelial lesion, and atypical  
glandular cells*, 48(1), 147-159.
- Spitzer, M., Apgar, B. S., & Brotzman, G. L. (2006). Management of histological abnormalities  
of the cervix. *American Family Physician* , 73, 105-112.
- Wright Jr., T. C., Massad, S., Dunton, C. J., Spitzer, M., Wilkinson, E. J., & Solomon, D. (2007).  
2006 Consensus guidelines for the management of women with abnormal cervical  
screening tests. *2006 ASCCP-Sponsored Consensus Conference: Vol. 11.* (pp. 202-222).
- Zsemlye, M. (2008). High-grade cervical dysplasia: pathophysiology, diagnosis, and treatment.  
In A. G. Waxman & W. F. Rayburn (Ed.), *Colposcopy, Cervical Screening, and HPV.*  
*Obstetric and Gynecologic Clinics of North America: Vol. 35,* (pp. 615-621).  
Albuquerque, NM: Elsevier.