UNIVERSITY OF CALGARY

Comparison of colposcopic impression, cervical punch biopsy histopathology, and final cervical excision histopathology and description of colposcopic practice in the management of cervical dysplasia in the Calgary Health Region

By

Anita Agrawal

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE

DEGREE OF MASTERS OF SCIENCE

DEPARTMENT OF COMMUNITY HEALTH SCIENCES

CALGARY, ALBERTA

AUGUST 2010

UNIVERSITY OF
CALGARY

UNIVERSITY OF CALGARY

FACULTY OF GRADUATE STUDIES

Abstract

Background:

Cancer of the cervix is an important issue in Canadian public health, with many women continuing to die in Canada, despite advances in detection and treatment. Cervical cancer usually develops gradually over many years from asymptomatic pre-cancerous changes in the lining of the cervix known as cervical dysplasia or CIN. On early diagnosis, cervical cancer has a very good prognosis (overall 74.0% 5year survival).

Study Objective:

The purpose of this study was to assess the degree of agreement between colposcopic impression, cervical punch biopsy histopathology, and final cervical excision procedure histopathology in women being investigated and treated for cervical dysplasia. The study also described the indications for final cervical excision procedure.

Method:

This was a retrospective chart review of 917 eligible women who had at least one prior positive diagnostic test (either cervical punch biopsy or ECC), and underwent final cervical excision biopsy procedure from January 2003 to December 2004 in CHR and an abnormal cervical punch biopsy histopathology or abnormal ECC histopathology. The kappa statistics was used to assess the degree of agreement and McNemar's Chi square test was used to assess the discordance between these procedures.

Results:

The degree of agreement was poor for all comparisons between diagnostic and / or therapeutic procedures. None of the 'k' values observed was higher than 0.26 (poor agreement). The false negative (undercall) rate for colposcopy compared to cervical

biopsy for HSIL was observed to be 60.8%, 52.2% for cervical biopsy compared to cervical excision procedure**,** and 66.2% for colposcopy compared to final cervical excision procedure. The PPV of colposcopy was 81.1% for the diagnosis of cervical dysplasia. In the majority (64.8%) of women, the indication for final cervical excision procedure was HSIL followed by LSIL (11.9%).

Discussion:

The results of this study are consistent with the previous reports and it highlights the discrepancies between the results of colposcopic impression, cervical punch biopsy, and cervical excision procedure histopathology. Lack of agreement between different diagnostic procedures could be due to inter and intraobserver variability in reporting of cervical dysplasia grade. More than one cervical biopsy is indicated to decrease the false negative rate of this procedure. Although this study design introduced verification bias and resulted in higher sensitivity and lower specificity than in a complete population sample, the research primarily set out to examine degree of agreement (k) between three diagnostic and / or therapeutic procedures, which is not affected by verification bias.

"See and treat in a single visit" approach could not be applied to this study cohort, as it would have resulted in overtreatment of 20.8% women and subsequent unnecessary complication. It would have also led under treatment of 66.2% women by not performing final cervical excision procedure for them based on colposcopic impression of LSIL, others, or negative (false negative).

Conclusion:

This study confirms that all three procedures are needed in the management of cervical dysplasia.

Acknowledgements

I would like to extend sincere thanks and gratitude to a few individuals for all of their effort, and for so generously giving their time and knowledge to assist me in this project.

I would like to especially thank Dr. Sue Ross for being such an incredible, patient, friendly, supportive, and attentive supervisor, without whom I would not have made it through this program. Throughout she provided me with invaluable comments and directed me. I would also like to greatly thank Dr. Jill Nation my clinical supervisor who taught me various skills during my fellowship training, provided advice and guidance for my thesis, and helped me with the departmental funding to assist in data base development. I would also like to extend sincere thanks and gratitude to Dr. M. Eliasziw for providing guidance especially for methods and results section of my thesis and Dr. Greg Nelson, a committee member, for reviewing my thesis.

My special thanks to Polya Ninova and Linda Kamhuka for helping in data collection and entry process and to Isabelle Xiong for her invaluable assistance with statistical analysis.

I wish to also thank all of the professors, teaching assistants, and administrative staff in the Department of Community Health Sciences, for their help and guidance throughout the program. Special thanks to Crystal Elliot for her assistance with all administrative issues.

Very special thanks to my husband Om Agrawal and my daughter Katyayni Agrawal for their support, help and encouragement along the way to complete the program.

Dedication

To my husband for his unconditional support and my three children who believed in me and trusted me to complete this work

Table of Contents

Approval Page ii

Abstract iii
Acknowledgements v
Table of Contents vii
List of Tables x
List of Figures and Illustrations xii
List of Symbols, Abbreviations and Nomenclature xiii
Epigraph xiv

CHAPTER 1: INTRODUCTION 1
Purpose and Objectives 4

CHAPTER 2: BACKGROUND 5
Introduction 5
Problem to be investigated 5
Incidence and outcome of cervical cancer 6
Pathogenesis of cervical dysplasia and cervical cancer 7
Detection and treatment of cervical dysplasia 10
Literature review 19
Method: 19
Comparisons of different methods of detection 20
Agreement between colposcopy, cervical punch biopsy histopathology, and cervical excision procedure (LEEP /cold knife cone) histopathology 25
Agreement between cytology, colposcopy, cervical punch biopsy histopathology, and cervical excision procedure histopathology 27
Agreement between colposcopy and cervical punch biopsy histopathology 28
Agreement between colposcopy and cervical excision procedure (LEEP / cold knife cone) histopathology 32
Agreement between cervical punch biopsy histopathology and cervical excision procedure (LEEP / cold knife cone) histopathology 33
Agreement of cytology, colposcopic impression, and cervical biopsy histopathology 35
Agreement between cervical cytology, cervical biopsy histopathology, and cervical excision procedure histopathology 36
Comparison between cervical cytology and colposcopy 37
Comparison between cervical cytology and cervical punch biopsy histopathology 38
Interobserver agreement studies for cytology and cervical punch biopsy histopathology 39
Quality assurance studies in regards to the performance of colposcopists and pathologists 43

Cervical Dysplasia Follow Up 43
Summary 52

CHAPTER 3 RESEARCH QUESTIONS 54
Primary Research Question 54
Secondary Research Question 54

CHAPTER 4 RESEARCH METHOD 55
Introduction 55
Study Design 55
Population Studied 56
Subject Identification 56
Inclusion Criteria 56
Exclusion Criteria 57
Details of Diagnostic Procedures 57
Data Collection and Management 58
Data Collection 58
Main Data Items 59
Data Management 61
Statistical Considerations: 61
Sample Size 61
Data Cleaning 62
Statistical Analysis 64

ETHICAL CONSIDERATIONS 72

CHAPTER 5: RESULTS 74
Characteristics of Study Sample 74
Test Results for the Study Cohort 78
Assessment of the degree of agreement of three diagnostic and / or therapeutic procedures 83
Colposcopic impression by cervical punch biopsy histopathology or ECC 83
Colposcopic impression by final cervical excision biopsy histopathology 85
Cervical punch biopsy histopathology and / or ECC by final excision biopsy histopathology 87

CHAPTER 6: DISCUSSION 90
Overview of the Discussion 90
Overview of the Findings and Clinical Implications 90
Agreement between colposcopic impression and final cervical excision procedure histopathology in comparison to other published studies 93
Explanation of poor degree of agreement between the procedures 97
Description of undercall and overcall in these procedures 100
Explanation of possible reasons for undercall and overcall in these procedures 102
Clinical use of the various diagnostic procedures 104

Characteristics of study population in comparison to other published studies 105
Results of studied procedures in comparison to other published studies 108
Status of margins of final cervical excision procedure specimen post procedure ECC in comparison to other published studies 111
Indications of final cervical excision procedure 112
Methodological Choices that may have Influenced Study Findings 113
Research Design 113
Lack of use of RCI for colposcopy interpretation 114
Procedures performance by novice versus expert 114
Absence of pathology review 115
Strengths and Limitations of the Study 116
Validity 116
Confounding 116
Bias 117
Verification bias 117
Selection bias: 119
Recall bias: 120
Study Strengths 121
Study Limitations 122
Appropriateness of the statistics and other tools used 124
"See and Treat" Clinics 125
Future Research Direction 127
Conclusion 128
References: 131
Appendix A: Description of Reid Colposcopy Index (RCI) and overall score and histology 156
Appendix B: Study Definitions 160
Appendix C: Map of the Calgary Health Region (Retrieved May 26, 2008. Available at http://www.calgaryhealthregion.ca/corporate/about_us/pdf/map.jpg) 168
Appendix D: Management of Cervical Dysplasia Study 169
Data Collection Form 169
Appendix E: Conjoint Health Research Ethics Board Approval Letter 180
Appendix F: Guidelines for Colposcopy Management CHR & TBCC 181
Appendix G: Management of Histological Abnormalities: Society of Canadian Colposcopists (SCC) guideline 185

List of Tables

Table 1: Natural History of Cervical Dysplasia (Ostor A.G, 1993) 9

Table 2: Pap Characteristics 11

Table 3: The 2001 Bethesda System Terminology for Cervical Cytology (Pap smear) ... 12

Table 4: Summary of Degree of Agreement and Percent Agreement Studies of Various Tests for Cervical Dysplasia Diagnosis and Treatment 21

Table 5: Summary of Percent Agreement and Degree of Agreement Studies of Observers for Various Tests for Cervical Dysplasia Diagnosis and Treatment 39

Table 6: Summary of Studies of Recommended Follow up After Cervical Excision Treatment for Cervical Dysplasia 45

Table 7: Level of Agreement as Determined by the Value of Kappa Statistics (Landis & Koch 1977) 66

Table 8: Study Cohort Demographics 75

Table 9: Referral Pap for Initial Colposcopy 76

Table 10: Test Results of Study Cohort 78

Table 11: Endocervical and Ectocervical Margin Histopathology of Final Cervical Excision Procedure 79

Table 12: Degree of Involvement of the Endocervical Gland in Final Cervical Excision Procedure 80

Table 13: Post Final Cervical Excision Procedure ECC Histopathology 81

Table 14: Comparison of Involved Endocervical Margin and Post Final Excision Procedure ECC Histopathology 81

Table 15a: Agreement between Colposcopic Impression and Cervical Punch Biopsy Histopathology 83

Table 15b: Agreement between Colposcopic Impression and Cervical Punch Biopsy Histopathology 83

Table 16a: Agreement between Colposcopic Impression and Final Cervical Excision Procedure Histopathology 85

Table 16b: Agreement between Colposcopic Impression and Final Cervical Excision Procedure Histopathology 85

Table 17a: Agreement between Cervical Punch Biopsy and Final Cervical Excision Procedure Histopathology 87

Table 17b: Agreement between Cervical Punch Biopsy and Final Cervical Excision Procedure Histopathology 87

Table 18: Reid Colposcopy Index 156

Table 19: RCI (overall score) Histology 158

List of Figures and Illustrations

Figure1: Flowchart of Different Tests Available for Cervical Dysplasia Management....10

Figure 2: Flowchart of the Possible Steps for Procedures and Tests in Colposcopy Clinic....18

Figure 3: Flowchart of the Follow-up Protocol after Final Cervical Excision Procedure in Colposcopy Clinic....44

Figure 4: Flowchart of the Calculation of the Final Sample Size....63

Figure 5: Flowchart of Steps of Combining Diagnostic Categories for Kappa Statistics Calculation....64

Figure 6: Number of Cervical Biopsies....77

List of Symbols, Abbreviations and Nomenclature

ACOG	American College of Obstetricians and Gynaecologists
ASCCP	American Society for Colposcopy and Cervical Pathology
AHS	Alberta Health Services
AIS	Adenocarcinoma-in-situ
CHR	Calgary Health Region
CHREB	Conjoint Health Research Ethics Board
CIN	Cervical Intraepithelial Neoplasia
CIS	Carcinoma in situ
ECC	Endocervical Curettage
FPR	False Positive Rate
FNR	False Negative Rate
HPV	Human Papilloma Virus
HSIL	High Grade Squamous Intraepithelial Neoplasia
LEEP	Loop Electrical Excision Procedure
LLETZ	Large Loop Excision of Transformation Zone
LETZ	Loop Excision of Transformation Zone
LSIL	Low Grade Squamous Intraepithelial Neoplasia
PPV	Positive Predictive Value
NPV	Negative Predictive Value
SCC	Society of Canadian Colposcopists
SCJ	Squamo-Columnar Junction
SIL	Squamous intraepithelial neoplasia
TBCC	Tom Baker Cancer Centre
TZ	Transformation Zone
WHC	Women's Health Centre

Epigraph

``Great discoveries and achievement invariably involves the cooperation of many minds``.

-Alexander Graham Bell

“If I have seen further than others, it is by standing upon the shoulders of giants.”

-Isaac Newton

CHAPTER 1: INTRODUCTION

Cervical cancer, a malignancy of the cells that line the surface of the cervix, continues to be of importance in Canadian public health. Many women continuing to die in Canada, despite advances in detection and treatment of precancerous lesions of cervix and cervical cancer. Cervica cancer usually begins as asymptomatic pre-cancerous lesions known as Cervical Intraepithelial Neoplasia (CIN) and or cervical dyaplasia, which develops gradually over many years. Cervical cancer has a very good prognosis (overall 74.0% 5-year survival) and with early detection and treatment, the mortality is even lower with 5-year survival more than 90.0% (Canadian Cancer Statistics, 2008).

A number of tests are used in sequence to detect and diagnose cervical dysplasia. The first screening test is *cervical cytology* in which cells are scraped off the cervix (the Papanicolaou (Pap) test. Three further tests are used in women where abnormal cells have been detected on Pap test:

- *Colposcopy* in which the cervix is examined visually using a "colposcope", an optical instrument that illuminates and magnifies the cervix after the application of 3 to 5% acetic acid;
- *Colposcopic directed cervical punch biopsy* in which biopsy samples are taken from the most atypical site of the cervix identified by the colposcopist; or *endocervical curettage* in which the mucous membrane of the endocervical canal is scraped and the sample is sent off for histopathology;

- *Cervical excision procedures* (Loop Electrical Excision Procedure (LEEP) biopsy, LEEP cone, and cold knife cone) in which cervical tissue is removed by a variety of excision technique and sent off for histopathological examination, are mainly used for the treatment of cervical dysplasia but can also be used in some cases for diagnosis purposes (Mousavi et al, 2007; Wright et al, 2002; Murdoch et al, 1992). The use of the cervical excision procedure is not without adverse consequences for some women, in terms of bleeding, infection, and interference in future fertility and pregnancy.

In order to best plan the ideal management for women with cervical dysplasia, it is important to understand the comparative characteristics of the various diagnostic and / or therapeutic procedures in clinical practice.

This study set out to examine, in the Calgary Health Region (CHR)[1], the agreement between the three diagnostic and / or treatment modalities for cervical dysplasia; colposcopic impression, cervical punch biopsy histopathology, and final cervical excision procedure histopathology using retrospective chart review of a cohort of women who underwent all three tests. If good agreement were observed between three procedures, it may be possible in a select group of patients (high risk group and poor compliance) to eliminate the need for colposcopic guided cervical punch biopsy thus

[1] After the end of data collection for this study, the nine health regions in Alberta (including CHR) were dissolved and combined to become Alberta Health Services (AHS) This thesis will refer to CHR, rather than AHS (Calgary zone).

making a “see and treat single visit” practice approach feasible, enabling simultaneous diagnosis and treatment of cervical dysplasia without compromising quality of care.

Purpose and Objectives

The purpose of this study was to assess the degree of agreement between colposcopic impression, cervical punch biopsy histopathology, and final cervical excision procedure histopathology (LEEP biopsy, LEEP cone biopsy, or cold knife cone biopsy histopathology) in women being investigated and treated for cervical dysplasia. It also describes the the indications for final cervical excision procedure.

CHAPTER 2: BACKGROUND

Introduction

The epidemiology of cervical dyaplasia, cervical cancer, various diagnostic methods for detection and treatment of cervical dysplasia and indications of final cervical excisional procedure will be discussed in this chapter. The relevant literature review is included in great detail. The follow-up of cervical dysplasia detection and management including relevant literature is presented in this chapter to help understand the whole process in the colposcopy clinic, however follow up will not be discussed in results and discussion section as it is not part of the study objective.

Problem to be investigated

Cervical cancer remains a significant problem in Canada despite advances in detection and management of precancerous lesions of the cervix and cervical cancer. Cervical cancer is a malignancy of the cells lining the surface of the cervix. It usually begins as asymptomatic pre-cancerous lesions and develops gradually over many years. It is the fourth most common female genital tract cancer in women age 15 to 29 and is the fourteenth most commonly diagnosed cancer among women of all ages in Canada; however it ranks third among women aged 20 to 49. Despite advances in screening techniques and treatment of precancerous lesion, in 2008, it is expected that 1,300

Canadian women will be diagnosed with cervical cancer and 380 will die from the disease (Canadian Cancer Statistics, 2008). In Alberta, 120 to150 cases of cervical cancer and approximately 1,500 cases of carcinoma in situ are diagnosed yearly, with up to 50 deaths. In 2002, 39 women died of invasive cervical cancer in Alberta (Alberta Cancer Statistics, 2007).

Incidence and outcome of cervical cancer

The incidence of cervical cancer in Canada is 7.0 per 100,000 women per year and in Alberta it is 9.0 per 100,000 women per year (Canadian Cancer Statistics, 2009). The mortality rate for cervical cancer is 2.0 per 1000 women in Canada, accounting for 1.2 % of cancer-related deaths in 2005 (Canadian Cancer Society, 2005; Canadian Cancer Statistics, 2009). The age adjusted incidence and mortality due to cervical cancer has decreased by 50.0% and 60.0% respectively since 1977, in part due to structured and improved screening strategies that accurately diagnose "precancerous lesions" which in turn results in early treatment (Munoz et al, 2003).

Cervical cancer has a very good prognosis (overall 74.0% 5-year survival), and following early detection and treatment the mortality is even lower, with 5-year survival of more than 90.0% (Canadian Cancer Statistics, 2008). Effective cervical cancer prevention requires recognition and treatment of cervical dysplasia. Colposcopy, cervical punch biopsy, and cervical excision procedure (e.g. LEEP, LLETZ) are the common

diagnostic tests for early detection of cervical dysplasia and to ensure that invasive disease is not missed (Hwang 1999; Wright et al, 2002; Mousavi et al, 2007).

Despite the improvement in detection, there is wide variation in clinician practice in relation to the types and sensitivity of tests used for the diagnosis of cervical dysplasia, and also in regards to the timing, schedule, and duration of follow up for women after cervical dysplasia has been detected and treated.

The current study analyzed the degree of agreement between colposcopic impression, cervical punch biopsy histopathology and / or endocervical curettage (ECC) and final cervical excision procedure histopathology. The study also investigated and described colposcopic practice in the CHR in terms of indications for cervical excision procedure (LEEP biopsy, LEEP cone, and / or cold-knife cone biopsy).

Pathogenesis of cervical dysplasia and cervical cancer

The leading etiologic factor in the pathogenesis of cervical dysplasia and invasive cervical cancer is infection with genital subtypes of human papilloma virus (HPV), transmitted by sexual contact (Kiviat N, 1996; Walboomers et al, 1999). HPV is a DNA double stranded virus and has more than 80 subtypes to infect humans. HPV is divided into two types: low risk type and high risk types (oncogenic). The persistence of high-risk HPV increases the risk of malignant transformation in the presence of other coexisting factors such as smoking, multiparity, and immunosuppression. The HPV infection is

extremely common; it is the most common sexually transmitted infection (STI) and is acquired within a short period from onset of sexual activity. Most of the infections are transient and the infection persists only in 5 to10.0% of cases (Franco, Duarte-Franco, & Ferenczy, 2001; Munoz et al, 2003; Moscicki et al, 2004). Incidence of the HPV infection ranges from 11.1% to 36.0%. The overall prevalence of HPV (any type) infection ranges from 10.8 to 29.0%, with the peak at around 25 years of age or younger. In addition to varying with age, HPV prevalence appears to vary with place of residence and ethnicity (e.g. first Nations women in Saskachewan, aboriginal women in Manitoba, and Inuit women) within Canada (Burk et al, 1996; Myers et al, 2000; Sellors et al, 2000; Brown et al, 2005).

Cervical cancer usually begins as an asymptomatic pre-cancerous lesion. CIN lesions are limited to the cervical epithelium and with the penetration of underlying basement membrane by neoplastic cells results in development of invasive cancer. These premalignant lesions of cervical squamous cell carcinoma, may persist over time unchanged, spontaneously regress to normal or a lesser grade of CIN, or progress to a higher grade of CIN or invasive carcinoma (Ostor A.G, 1993). Rates of progression correlate directly with the CIN grade **(Table 1, overleaf).** The long natural history provides the opportunity for screening to effectively detect this process during the cervical dysplasia phase, thus allowing early treatment and cure. Several tests are required to screen and diagnose cervical dysplastic lesions: cervical cytology, colposcopy, colposcopic guided cervical punch biopsy histopathology (Nasiell et al, 1986; Nash et al, 1987; Bosch et al, 1995; Kiviat 1996; Alani et al, 1998; Ho et al, 1998; Melnikow et al,

1998; Holowaty et al, 1999; Wallin et al, 1999; Walboomers et al, 1999; Soloman et al, 2002).

Table 1: Natural History of Cervical Dysplasia (Ostor A.G, 1993)

	Regress	**Persist**	**Progress to CIS**	**Progress to invasion**
CIN I	60.0%	30.0%	11.0%	1.0%
CIN II	40.0%	40.0%	20.0%	5.0%
CIN III	33.0%	56.0%		12.0% (10- 20.0%)

Detection and treatment of cervical dysplasia

A variety of tests are used to screen, diagnose, and treat cervical dysplasia, with cervical excision procedure histopathology being the definitive modality **(Figure 1).**

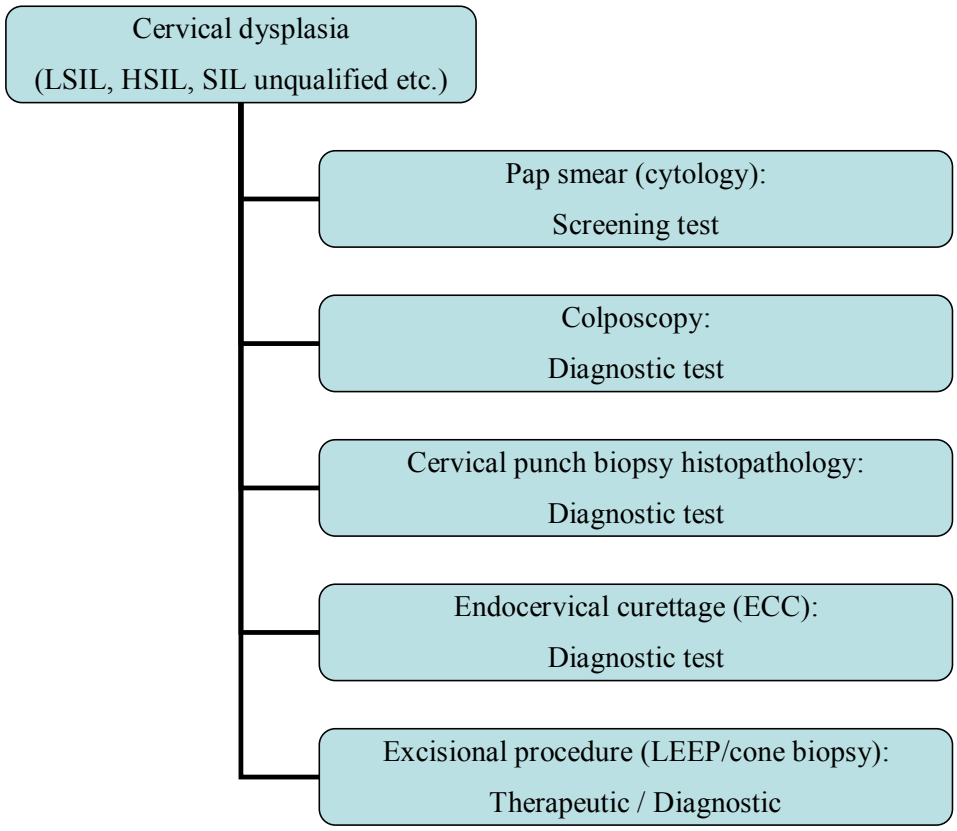


Figure1: Flowchart of Different Tests Available for Cervical Dysplasia Management

Cervical Cytology (Pap smear) is a screening test in which cells are scraped off the cervix, then stained and examined under a microscope for cytological changes in the cervix. This test is also called the Papanicolaou test, more commonly known as the "Pap test". Cervical lesions are described according to the degree of cytopathology found on Pap smear. It is a screening test and its sensitivity for various cytological abnormalities is described in **(Table 2, below).**

Table 2: Pap Characteristics

Pap test	Disease identified	Sensitivity (%)
HSIL	CIN 2/3 or cancer	60
LSIL	CIN 1	59
ASC-US	CIN 2/3 or cancer	9
ASC-US	CIN 1	20
AGC	Any CIN or adenocarcinoma	11
SCC	Invasive cancer	48

The CIN grading system has been gradually replaced by the Bethesda System, which was initially introduced in 1989. A newer terminology for cervical cytology was adopted in the 2001 Bethesda system **(Table 3, overleaf)**, which is the most internationally accepted system for classification of Pap smear (Solomon et al, 2002).

Table 3: The 2001 Bethesda System Terminology for Cervical Cytology (Pap smear)

Squamous Cell Abnormalities	Negative for Intraepithelial lesion (NIL)
	Atypical squamous cells (ASC)
	Atypical squamous cells of undetermined significance (ASC-US)
	Atypical squamous cells cannot exclude HSIL (ASC-H)
	Low-grade squamous intraepithelial lesion (LSIL) encompassing: human papilloma virus / mild dysplasia / cervical intraepithelial neoplasia (CIN) 1
	High-grade squamous intraepithelial lesion (HSIL) encompassing: moderate and severe dysplasia, carcinoma in situ; CIN 2 & CIN 3
	Squamous cell carcinoma (SCC)
Glandular Cell Abnormalities	Atypical glandular cells (AGC)
	Atypical glandular cells, favor neoplastic
	Endocervical adenocarcinoma in situ (AIS)
	Adenocarcinoma

Colposcopy is not a screening test, it is a visual examination of the cervix using "colposcope", an optical instrument that illuminates and magnifies the cervix. The standard protocol for colposcopy includes conventional visual assessment, application of 3 to 5.0% acetic acid and identification of the squamo-columnar junction (SCJ) and transformation zone (TZ). The goal is to identify the most atypical site or abnormal area for biopsy in patients with an abnormal cervical smear. "Colposcopic Impression" is the

classification given to the appearance of cervix uteri visualized through colposcope (Hopman, Kenemans, & Helmerhorst, 1998). Currently, colposcopy is recommended for women with low-grade squamous intraepithelial lesion (LSIL) or worse cytology (ASC-H, HSIL, AIS) and atypical squamous cells of undetermined significance (ASC-US) that persists or is associated with high-risk human papilloma virus (HPV) infection. The colposcopy examination is aimed at detecting cervical dysplasia, especially CIN 3, which can then be treated to prevent cervical cancer. A further goal is to ensure that a potential diagnosis of invasive cancer is not missed. Colposcopic evaluation is a visual technique affected by observer subjectivity (Benedet et al, 1985; Buxton et al, 1991; Sideri et al, 2004; Gage et al, 2006; Jeronimo & Schiffman, 2006) and its accuracy varies according to the skill and experience of the colposcopists. Colposcopy requires extra training and experience. Regular performance of this procedure is necessary to maintain the skill (Mitchell et al, 1998). Colposcopy allows for the identification of specific colposcopic features that distinguish between normal, benign, preinvasive, or invasive disease (Burghardt E 1991; Anderson et al, 1996). Histopathological diagnosis is considered gold standard in defining the diagnostic accuracy of colposcopic impression (Hopman et al, 1995; Benedet, Matisic, & Bertrand, 2004). Using histopathology, the sensitivity of colposcopy for cervical abnormalities is high at 96.0 to 97.0% but specificity is low at 48 to 54.8% (Kirkup & Hill, 1980; Mariamma et al, 1991; Hopman et al, 1995; Jeromino & Schiffman, 2006). Gage et al. (2006) reported that the combined sensitivity of colposcopy for diagnosing HSIL increased to 83.3% from 68.3% when more than one cervical biopsy was taken.

Cervical Punch Biopsy Histopathology is the microscopic examination of biopsy samples taken from the most atypical site of the cervix identified by the colposcopist. Colposcopy with directed cervical punch biopsy histopathology is the critical diagnostic step (Veridiano, Delke, & Tancer, 1981) for women with cervical cytological abnormalities and serves a key role in screening programs. Colposcopic guidance of biopsies increases the predictive value for microinvasive and invasive disease considerably, despite its limitations in defining the extent and severity of epithelial lesions. The grade of the lesion may vary in different parts of the same cervix; therefore it may not sample the worst histological grade of CIN present. It also misses a fair percentage of HSIL especially if the lesion is small. Because the colposcopic appearance may be complex and the most abnormal area may quite small, more than one biopsy is indicated to increase the sensitivity (Gage et al, 2006; Jeronimo & Schiffman, 2006). Gage et al. (2006) advised taking additional biopsy specimens from a second worst looking area, an abnormal looking area, and / or random biopsy of normal looking cervix. The severity of the cervical biopsy result directs the clinician towards the appropriate treatment of precancerous lesions.

Endocervical Curettage (ECC) is a procedure in which the mucous membrane of the endocervical canal is scraped using a spoon-shaped instrument called a curette and the specimen is sent in formalin to be examined under microscope by a histopathologist. Endocervical sampling may be obtained with vigorous endocervical brushing: the sensitivity of this sampling method is similar to that of using the curette (ACOG practice bulletin, 2008). Disadvantages of ECC include discomfort, high false positive rate, and

high false negative rate. In the case of positive ECC, the true incidence of endocervical disease is low; it varies from 18.9% to 27.3 % (Naumann et al, 1996).

The ACOG public bulletin (2008) recommends the omission of ECC with initial colposcopy. In the case of ASC and LSIL, ECC is only indicated at the time of colposcopy if examination is unsatisfactory, if ablative treatment (cryotherapy or laser ablation) is considered, and in conjunction with cone biopsy in cases of AGC, AIS, ASC-H, and HSIL on Pap smear, or if an cervical excision procedure (LEEP biopsy, LEEP cone, or cold knife cone biopsy) is being done. ACOG recommends performing ECC at the time of the excision procedure to check the completeness of excision of cervical dysplasia lesion. It should also be considered in cases of repeat excision procedure for incompletely treated HSIL (Abu & Davies, 2005). The American Society for Colposcopy and Cervical Pathology (ASCCP 2001) guidelines suggest that performing ECC at the end of the cervical excision procedure is not mandatory. Positive ECC (when dysplastic cells are present in ECC specimen) and positive margin (when abnormal cells are found at the edge of the final excision biopsy sample) implies the presence of residual disease (Barnes et al. 1998). The combination of a positive margin of the LEEP specimen with a positive ECC indicates up to an eight-fold greater chance of residual CIN or invasive disease (Soutter et al, 1997; Bornstein et al, 2004). Fine et al. (1998) retrospectively evaluated pre- and postoperative value of ECC in 391 charts of women who had cervical conization performed and found good agreement between grade of cervical dysplasia on preoperative ECC and subsequent conization. They recommended routine use of ECC prior to conization and stated that it was of no value to detect residual dysplasia, in contrast to the

ACOG recommendations. Naumann et al. (1996) evaluated the need for routine ECC during colposcopy by reviewing 341 charts and concluded ECC could safely be omitted in patients with adequate colposcopy, as well as for patient who will require an excision biopsy procedure. In Calgary, ECC is performed routinely with all colposcopies.

Cervical Excision Procedure Histopathology involves the microscopic examination of tissue samples obtained with LEEP cone, cold knife cone, or LEEP biopsy by a pathologist. This test is the gold standard for the diagnosis of cervical intraepithelial neoplasia and can diagnose invasion in those with negative colposcopic im pression and / or directed biopsy (Burger & Hollema, 1993). The excision biopsy procedure is not only diagnostic but therapeutic as well. This modality is a conservative modality to treat cervical dysplasia. The rationale for conservative treatment of cervical dysplasia is to prevent the development of invasive cancer without performing a hysterectomy to remove the uterus and cervix. Excision biopsy is performed in cases of persistent LSIL, HSIL, AIS, ASC-H, suspected microinvasive carcinoma, positive ECC, unclear diagnosis, and significant disagreement between Pap smear, colposcopic impression, and cervical punch biopsy. The increasing use of excision procedure has resulted in two potential clinical problems: the removal of excess amount of tissue and the possibility of over treatment of cervical dysplasia. Ferenczy, Choukroun, & Arseneau (1996) in Montreal evaluated the advantages and pitfalls of the LEEP in 1189 consecutive women who underwent the conization procedure. The researchers found a 7% (71 women) complication rate. Half of these women developed acute complications like bleeding and infection. The authors also found that only 14% of the LEEP specimens were negative, whereas several other studies

have reported negative rates between 5 to 40% (Luesley et al, 1990; Denny et al, 1995; Ferenczy et al, 1996; Maluf et al, 2004). The cervical excision procedure is not a benign procedure and it is associated with morbidities which include bleeding (4.3 to 14.0%), cervical stenosis (1.3 to17.0%), infertility (4.0%), future cervical incompetence (premature labour), and infection (Ohel et al, 1981; Luesley et al, 1990; Barker et al, 2001; Chappatte et al, 1991; Lopes et al, 1994; Kietpeerakool et al, 2006; Jakobsson et al, 2007; Arbyn et al, 2008). Dunn et al. (2004) reported an overall complication rate of 9.7 %, with a major complication rate of 0.6%, in a retrospective chart review of 574 women who underwent LLETZ. Rarely vesico-vaginal fistula formation has been reported (Krissi et al, 2001).

To summarize, the approach of investigation and management of women with cervical dysplasia is a stepped process **(Figure 2, page 18)**. Initially Pap smear is used to screen women followed by colposcopic examination of those women whose Pap smear is reported as abnormal. If colposcopic impression is not negative then suspected cervical lesions are biopsied under colposcopic guidance and sent for histopathological examination. If there is no visible lesion on colposcopy and Pap smear was abnormal, women may undergo ECC. Based on histopathology of colposcopic guided cervical punch biopsy or of ECC women will be advised to undergo final cervical excision procedure. At each step women may receive a negative diagnosis and follow up colposcopy advised; or receive a positive diagnosis and be advised to have treatment (final cervical excision procedure); or else receive an unclear diagnosis and go on to have excision procedure as a diagnostic test. Thus at each step women with negative diagnoses can be removed from further diagnostic processes and sent for routine screening. The goal is to perform invasive

procedures (LEEP, LEEP biopsy, cold knife cone) only in women with severe cervical dysplasia (HSIL), unclear diagnosis, or if concern is about missing invasive cervical cancer, in order to avoid inherent adverse outcomes associated with a cervical excision procedure.

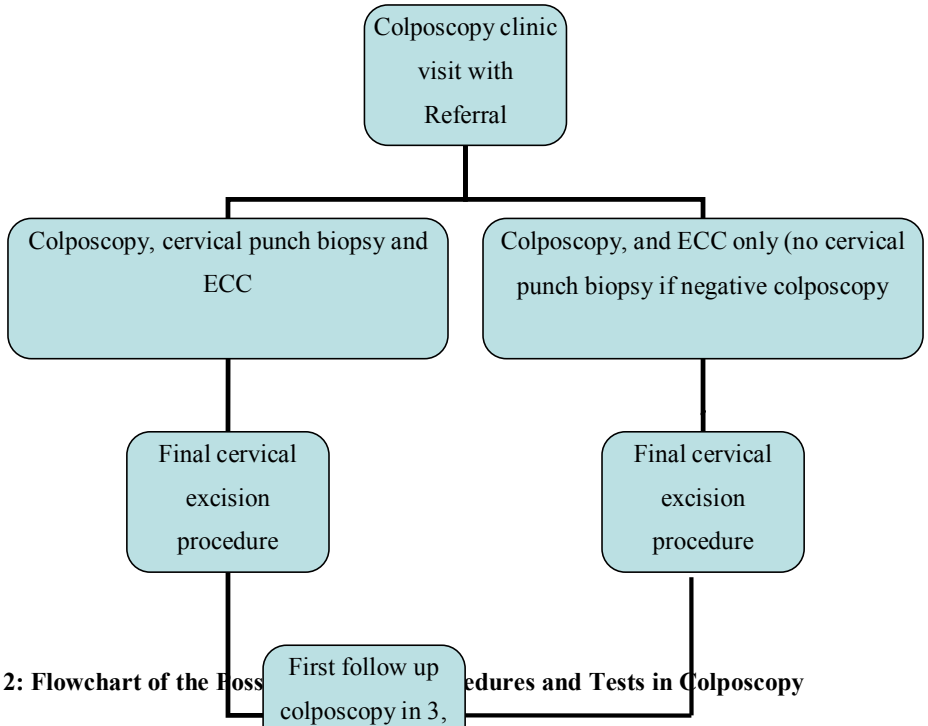


Figure 2: Flowchart of the Possible Procedures and Tests in Colposcopy Clinic

In order to manage cervical abnormalities when appropriately, it is necessary to diagnose accurately, and thus ensure that they receive optimal treatment and follow up. It has been suggested that an important approach to the variability of colposcopic practice is to correlate the colposcopic impressions with cervical excision procedure histopathology (LEEP biopsy, LEEP cone biopsy). Several studies in colposcopy have compared colposcopic impressions with histopathology in

addition to comparison with cytology **(Table 4, page 22 to 25).** These will be described and discussed in the following section of the thesis.

Literature review

Method:

A search of the English literature in the Medline and the Embase databases " from 1966 to 2009 was carried out using the key words "cervical intraepithelial neoplasia", "cervical dysplasia", "precancerous cervical lesion", "cervical cancer", "colposcopy", "cervical punch biopsy", "LEEP", "cervical conization", "observer agreement", "agreement", "percent agreement", and "correlation. Articles were also searched by combining the key words "colposcopy", "cervical punch biopsy", and "LEEP", "cervical conization" with key words "diagnosis", "management", "positive predictive value", and "negative predictive value". "Google scholar" search engine was also used with various combinations of key words used to identify relevant articles, such as "correlation between cervical biopsy, colposcopy, and or LEEP". The references from the identified articles were searched and also included.

Comparisons of different methods of detection

Several previous studies have assessed the agreement between screening and different diagnostic tests. The authors in these studies assessed agreement between cervical cytology, colposcopy, cervical punch biopsy histopathology, and final cervical excision procedure histopathology in various combinations, finding varying degrees of agreement**.** The majority of the studies did not examine the degree of agreement, rather examining percent agreement between pairs of modalities; colposcopic impression, cervical punch biopsy histopathology, and final cervical excision procedure histopathology. The majority of studies were done in the USA and Europe: very few were carried out in Canada and none in Alberta **(Table 4, page 22 to 25)**.

Following the table, studies are discussed in groups, where agreement between test results has been presented as follows:

colposcopy, cervical punch biopsy histopathology, and cervical excision procedure histopathology **(page 26 to 27)**; cervical cytology, colposcopy, cervical punch biopsy histopathology, and cervical excision procedure histopathology **(page 28)**; colposcopy and cervical punch biopsy histopathology **(page 29 to 32)**; colposcopy and cervical excision procedure histopathology **(page 33)**; cervical punch biopsy histopathology and cervical excision procedure histopathology **(page 34 to 35)**; cytology, colposcopic impression, and cervical biopsy histopathology **(page 36**); cervical cytology, colposcopy and cervical

excision procedure histopathology **(page 37 to 38)**; cervical cytology and cervical punch biopsy histopathology **(page 378**; and cervical cytology and cervical excision procedure histopathology **(page 39).**

Table 4: Summary of Degree of Agreement and Percent Agreement Studies of Various Tests for Cervical Dysplasia Diagnosis and Treatment

Type of Study	Author / Date	Country	Size	Main Data Items	Main Results
Colposcopy, cervical punch biopsy histopathology, and cervical excision procedure histopathology					
Retrospective	Spitzer et al. /1998	USA	604/ 233	Colposcopy, colposcopic guided CPBx, cone HPL	AGT 74.5% between cytology, CPBX HPL & cone HPL for HSIL
Retrospective	Ngan et al. / 1993	Hong Kong	103	Colposcopy, colposcopic guided CPBx, & LETZ HPL	AGT of 76.7% between colposcopy & CPBX HPL: 74.5% AGT between colposcopy & LETZ HPL: no agreement between CPBx & LETZ
Retrospective	Denny et al. / 1995	South Africa	298 184 A 114 B	Colposcopy, CPBx, and LLETZ HPL (A) Colposcopy & LLETZ HPL (B)	Overall AGT 82.0% in group A (116 had cone, 61 had negative biopsy) & overall percent AGT 85.0% in group B
Prospective	Boelter & Newman / 1974	USA	102 67 47	Colposcopy, CPBx HPL, cone HPL	Perfect AGT in 97.8% between CPBx HPL & cone HPL in 47 patients

Formatted Table

Type of Study	Author / Date	Country	Size	Main Data Items	Main Results
Cytology, Colposcopy, cervical punch biopsy histopathology, and cervical excision procedure histopathology					
Prospective	Higgins et al. / 1994	USA	188	Pap smear, Colposcopy, CPBx, & LEEP	AGT of 57.0 %, between CPBx & LEEP for HSIL., AGT of 89.0% between Pap and colpo for LSIL and 32.0% for HSIL, k = 0.29 for CPBx & LEEP, k =0.09 for colpo & CPBX
Prospective	Ihonor et al, / 1999	UK	100	Cytology, colposcopy, CPBx, & LLETZ	AGT of 61.0%, & K = 0.20, between CPBx & LLETZ. AGT of 83% between colpo and LLETZ for HSIL, & AGT of 62% between cytology and LLETZ
Colposcopy and cervical punch biopsy histopathology					
Prospective	Mousavi et al. / 2007	Iran	353	Colposcopy & CPBx HPL between RCI & GC	Between colposcopy & CPBx HPL , k= 0.74 for RCI group versus k= 0.45 for GC group, p = <0.001 for both group
Prospective	Baum et al. /2006	USA	456	Colposcopy & CPBx HPL between residents & nurse practitioners	Perfect AGT in 32.0%, within one degree AGT in 77 % of CPBx HPL & colposcopy & k = 0.19 & p = < 0.001. k highest for nurse practitioners & lowest for R3
Prospective	Massad & Collins / 2003	USA	2,825	Colposcopy & CPBx	Exact AGT in 37.0% & agreed within one grade in 75% between colposcopy & CPBx, p= <0.001, k=0.20

Formatted Table

Type of Study	Author / Date	Country	Size	Main Data Items	Main Results
Colposcopy and cervical punch biopsy histopathology (continued)					
Prospective	Sheshadri et al. / 1999	USA	92	Colposcopy & CPBx HPL for residents & faculty	For both residents & faculty; k = 0.56
Retrospective	Korkolop-oulou et al. /1992	Greece	108	Colposcopy & CPBx HPL	Exact AGT in 24.2% & within one grade in 45.1%, between colpo & CPBx HPL
Prospective	Chappatte et al./1991	UK	100	CPBx & LEEP HPL	Exact AGT in 42.0% between CPBx HPL & LEEP HPL
Colposcopy and cervical excision procedure histopathology					
Retrospective	Szurkus & Harrison / 2003	USA	104	Colposcopy & LEEP HPL	Exact AGT in 32.0% for colposcopy & LEEP HPL & 70.0% had AGT within one degree
Retrospective	Lenehan et al. / 1987	UK	58	Colposcopy & CPBx HPL	AGT within one degree in 84.5% of cervical conisation & colposcopy
Cervical biopsy histopathology and cervical excision procedure histopathology					
Prospective	Boonlikit et al. 2006	Thailand	352	Colposcopic directed CPBX HPL & LLETZ	Between CPBX HPL and LLETZ HPL; k = 0.24 & p = <0.0001, and in women > 50 yrs of age; k = 0.31, & p = <0.001
Retrospective chart review	Barker et al. / 2001	USA	448	CPBx & LEEP HPL	Exact AGT in 45.0 % & agreed within one grade in 80.1%, k = 0.73, p=<0.0001
Retrospective	Yarnoz et al. / 1988	Spain	81	CPBx HPL & cone HPL	Perfect AGT in 68.0 % of CPBx HPL & cone HPL

Type of Study	Author / Date	Country	Size	Main Data Items	Main Results
Cervical cytology, colposcopic impression, and cervical biopsy histopathology					
Retrospective	Benedet et al. / 2004	British Columbia	84,244	Cytology , colposcopy, & CPBx HPL	Within one degree 90.0% correlation between cytology & colposcopy, k = 0.56, & 82.0% between cytology & biopsy, k =0.42, p=<0.001.
Prospective	Massad, Collins, & Meyer / 2001	USA	1842	Cytology, colposcopy & CPBx	Exact AGT 35.0% between cytology & CPBx in & 61.0% AGT between CPBx & LLETZ (k = 0.20)
Cervical cytology, cervical biopsy histopathology, and cervical excision procedure histopathology					
Retrospective	Cetzin et al. / 1998	USA	280	Cytology, CPBx, and Cone biopsy	Exact AGT in 56.5% of cone HPL & cytology & AGT within one grade in 92.3%. Exact percent AGT in 40% of cone HPL & CPBx & AGT within one grade in 69.4%
Prospective	Heatley & Burke, 1998	UK	107	Cytology, CPBx, and Cone biopsy	Exact AGT in 63.0% , and AGT within one degree of 95.0% for cone HPL & CPBx. Exact AGT of 49.0% &AGT within one degree of 90.0% for cone HPL & cytology
Retrospective	Ang et al. / 1995	USA	242	Pap smear, CPBx HPL & LETZ HPL	Exact AGT in 67.0% of LSIL & 79.0% on HSIL on CPBx & within one grade in 83.0% between CPBx & LETZ HPL

Formatted Table

Abbreviations: RCI= Reid colposcopic index; GC = general colposcopy; CPBx = cervical punch biopsy; HPL = histopathology; AGT = Percent agreement. Kappa (k) = degree of agreement

Agreement between colposcopy, cervical punch biopsy histopathology, and cervical excision procedure (LEEP /cold knife cone) histopathology

Four studies examined all three tests used for diagnosis and treatment.

In a study by (Spitzer et al, 1998) involving 604 women, 277 (74.5%) out of 371 women with HSIL preoperatively (colposcopy / cervical biopsy / ECC) were found to have HSIL on cone histopathology, compared to 49 (21.0%) of 233 women that were believed to have CIN 1 by colposcopic impression, but found to have CIN 2 or CIN 3 on the final excision biopsy specimen from directed cervical biopsies. These findings indicated a good percent agreement for HSIL for both techniques with the final histopathology. The authors reported that their findings were similar to agreement reported by (Higgins et al, 1994) and (Skehan et al, 1990) between colposcopic impression and LEEP.

Ngan et al. (1993) examined the percent agreement between colposcopic impression, colposcopic guided cervical punch biopsy, and (LETZ) in 108 women. They reported 76.7% agreement between colposcopic impression and cervical punch biopsy histopathology, and 74.5% agreement between colposcopic impression and LETZ histopathology. Agreement between cervical punch biopsy histopathology & LETZ histopathology was not reported.

Denny et al. (1995) evaluated the role of cervical punch biopsy in overtreatment with Large Loop Excision of Transformation Zone (LLETZ) in two groups of women. In "group A", colposcopy, cervical punch biopsy, and LLETZ was performed and "group B" patients underwent only colposcopy and LLETZ. Overall percent agreement of 82.0% was noted in group A (116 had cone, 61 had negative biopsy) and 85.0% agreement in group B. Overall 25% of all negative punch biopsies were false negative when compared to LLETZ histopathology. Overall negative histopathology after LLETZ was not statistically different between the two groups and the authors concluded that cervical punch biopsy of the cervix does not reduce negative histopathology after LLETZ.

Boelter & Newman (1975) examined the percent agreement between colposcopic impression, colposcopic directed punch biopsy histopathology, and conization in 47 women and found identical results for the directed biopsy and conization in all except one case. However, the authors did not look for the degree of agreement with colposcopic impression and had excluded patients with negative colposcopy and negative cervical punch biopsy histopathology, this study was limited due to selection bias.Two out of above four studies had very small sample sizes, and in addition the authors did not analyse the percent agreement for all three modalities to each other. None of these studies authors assessed degree of agreement (k), which is a robust statistic tool for that purpose.

Agreement between cytology, colposcopy, cervical punch biopsy histopathology, and cervical excision procedure histopathology

Higgins et al. (1994) performed a prospective study on 188 women with abnormal Pap, and all those women underwent colposcopy, colposcopic directed cervical biopsy, and LEEP histopathology and noted agreement of 89.0% between Pap and colposcopy for LSIL and 32.0% for HSIL. The authors observed k of 0.29 for cervical biopsy and LEEP and k of 0.09 for colposcopy and cervical biopsy and concluded that there is discrepancy between cervical biopsy and cone histopathology and treatment should be individualized.

Ihonor et al. (1999) performed a prospective study on 100 women to assess correlation between cytology, colposcopic directed cervical biopsy and LLETZ. The authors noted 61.0% percent agreement and k = 0.20 between Cervical biopsy and LLETZ and agreement of 83.0% between colposcopy and LLETZ for HSIL. The authors also assessed waiting time for colposcopy appointment and found mean waiting time of 7.0 weeks for HSIL cytology. The authors also assessed the rate of overtreatment (9.0%) in selected population (unsatisfactory colposcopy) by see and treat policy and concluded see and treat policy should be reserved for this population. The authors also reaffirmed reported discrepancy between, cytology, colposcopic impression, cervical biopsy, and cone histopathology.

Agreement between colposcopy and cervical punch biopsy histopathology

Six studies evaluated agreement between colposcopy and cervical punch biopsy histopathology.

Mousavi et al. (2007) performed a prospective study on 344 women to determine the degree of agreement between colposcopic impressions using the Reid Colposcopic Index (RCI) and retrospectively compared this with a previous study done on 353 women by the same colposcopists, using the general scoring (GC) system. The RCI is a systematic, objective method of colposcopically grading the severity of precancerous lesions of the cervix (Reid and Scalzi, 1995; Ferris D.G, 2010). The index considers four colposcopic signs: lesion margin, color of acetowhitening, blood vessels, and iodine staining and permits differentiation between low grade and high grade lesion. Each sign is assigned a numerical value, and the scores are combined to establish the total RCI score. The value of the total score is used to estimate the severity of disease, with low scores representing low severity **(Appendix A, Table 18 &19).** The authors reported the degree of agreement (k) was 0.74 between colposcopy and cervical biopsy histopathology for RCI group versus k of 0.45 for GC group. The study concluded that RCI produced higher agreement with cervical punch biopsy histopathology and is reproducible, so it should be taught and used to evaluate colposcopy. In this study the two different scoring systems were used in two different groups of women, who may have different degree of cervical dysplasia and which may have affected the study result.

Baum et al. (2006) assessed the accuracy of colposcopic impression of gynaecology residents at various levels of training, and nurse practitioners, by comparing it with cervical biopsy histopathology in 456 women. The authors reported poor agreement overall, with perfect percent agreement in only 32.0%, and agreement within one degree in 77.0 % of cervical punch biopsy histopathology and colposcopy. The degree of agreement determined by k statistics was 0.19. Degree of agreement was highest (k=0.38) for the nurse practitioners and lowest (k=0.11) for third year residents and it was concluded that there was little difference in the accuracy of colposcopy between residents at different levels of training.

In a colposcopic agreement study done by Massad & Collins (2003) in the USA involving 2825 women, exact percent agreement was detected between colposcopic impression and biopsy in 37.0% of the cases (n = 893) and results agreed within one grade in 75.0% of them. In their population, 40.0% of the reports based on colposcopy overestimated the severity of cervical disease while 23.0% underestimated it. Based on these results, the authors concluded that colposcopic impression alone was imprecise.

Sheshadri & O'Connor (1999) compared the agreement of colposcopic impression between residents and faculty colposcopists and their ability to predict severity of disease at colposcopic directed cervical biopsy results in 92 patients. The degree of agreement for colposcopic impression was k=0.56 for both residents and faculty colposcopists. Both groups of examiners identified CIN2 and CIN 3 lesion with 78 to 82.0% accuracy. For all other lesions accuracy dropped to 60 to 63.0% and authors concluded that in higher grade

lesions, colposcopy can accurately predict abnormality but directed biopsy is necessary for definitive diagnosis. This conclusion is similar to that of (Hopman, Kenemans & Helmehorst, 1998) in their overview of all relevant studies for the period of 1972 to 1995, finding that the PPV value of the colposcopic impression increases with the severity of grade of premalignant cervical lesion, and directed cervical biopsy further increases its PPV. Due to the absence of the characteristic histological features, microinvasion is the most difficult to diagnose by colposcopy and up to 50.0% of cases were missed.

Korkollopoulou et al. (1992) correlated colposcopic findings with histopathological proven cervical dysplasia or condylomata changes in 108 women, and found sensitivity of 89.0% for cervical dysplasia and 61.0% for condylomata changes, but 45% under-diagnosis of cervical dysplasia on colposcopy. The authors supported the necessity of biopsy in conjunction with colposcopy to establish the definitive diagnosis for management.

Chappatte et al. (1991) studied the percent agreement between colposcopic impression and colposcopic directed biopsy histopathology in 100 women, and found 24.0% underestimation and 32.0% overestimation in the colposcopic impression group versus 16.0% underestimation and 41.0% overestimation of cervical dysplasia in the colposcopic biopsy group. The authors did not include agreement with cervical excision procedure histopathology.

In summary, in all these studies the authors reported moderate to poor percent agreement between colposcopic impression and cervical biopsy histopathology and improved percent agreement for higher grade lesions. Most of the studies noted that experience of the colposcopists plays only a small role in the overall performance and necessity of cervical biopsy was emphasized.

Agreement between colposcopy and cervical excision procedure (LEEP / cold knife cone) histopathology

Two studies examined agreement between colposcopy and cervical excision procedure findings.

Szurkus & Harrison (2003) examined the correlation between colposcopy and LEEP histopathology in 104 women who did not have cervical biopsy done. The authors reported 32.0% exact percent agreement and 70.0% agreement within one degree for colposcopy and LEEP histopathology. They concluded that despite poor agreement, HSIL on Pap is an appropriate indication for LEEP without performing cervical biopsy to confirm the diagnosis.

Lenehan et al. (1987) correlated cervical _onisation histopathology with colposcopic impression in 58 women and found 84.5 % percent agreement within one degree. In this study colposcopy missed microinvasive carcinoma in five women. The authors concluded that in the majority of cases, colposcopy is reliable in predicting the severity of lesion and can be used to decide definitive treatment.

Both of these studies have small sample sizes and although good to excellent percent agreement was noted within one degree, exact percent agreement measured in one study was poor.

Agreement between cervical punch biopsy histopathology and cervical excision procedure (LEEP / cold knife cone) histopathology

Three studies reported agreement between cervical punch biopsy histopathology and cervical excision procedure histopathology.

Boonlikit et al. (2006) assessed the accuracy and correlation between colposcopic directed cervical biopsy histopathology and LLETZ in 352 women. The authors found overall poor correlation (k=0.24) between biopsy histopathology and LLETZ histopathology. Degree of agreement was somewhat better (k=0.31) in a subgroup of women over 50 yrs of age. The authors concluded that cervical punch biopsy is not a reliable diagnostic tool in younger women and correlation between satisfactory colposcopy and biopsy histopathology is better in older women (over 50 yrs of age).

Barker et al. (2001) performed a retrospective chart review of 448 women and found 45.0% exact percent agreement between cervical punch biopsy and LEEP histopathology, and 84.0% agreement between cervical punch biopsy histopathology and LEEP specimen histopathology when compared within one degree. They noted 7.0% of the LEEP histopathology as normal (cervical biopsy overcall). They did not look for agreement between colposcopic impression, cervical punch biopsy histopathology, and final excision procedure histopathology.

Yarnaz et al. (1988) investigated the correlation between colposcopic directed cervical biopsy histopathology and cone biopsy histopathology in 81 women for cervical dysplasia and reported perfect percent agreement in 68.0 % of cases. They also reported haemorrhage and infection as the two main complications _onisation_ion as reported in other literature (Chappatte et al, 1991; Ferenczy et al, 1996; Barker et al, 2001).

In summary, in all these studies the authors have examined the percent agreement between cervical biopsy histopathology and cervical excision procedure histopathology and found exact percent agreement to a moderate degree and excellent agreement within one degree. Only Boonlikit et al. (2006) used kappa statistic to analyze degree of agreement and found poor agreement. These studies demonstrate that different degrees of percent agreement were likely due to different population characteristics and different clinical practices. Moreover, a review of colposcopic studies indicates that in 1to10% of cases, lesions more severe than anticipated by biopsy are found at excision (ACOG: Practice bulletin, 2005). This is confirmed by several studies comparing colposcopic directed cervical punch biopsy to "_onisation". These studies also demonstrate a significant rate of under diagnosis with cervical punch biopsy histopathology (ACOG: Practice bulletin, 2005). On the other hand, cervical punch biopsies that overestimate the grade of CIN are associated primarily with over-treatment (Costa et al, 2003).

Agreement of cytology, colposcopic impression, and cervical biopsy histopathology

Benedet, Matisic & Bertrand (2004) performed a retrospective review of 84,244 patients to determine the correlation between referral cytology, initial cervical biopsy, and colposcopic impression. They found 90.0% correlation between referral cytology and colposcopic impression within one degree and 82.0% correlation within one degree between referral cytology and cervical biopsy histopathology. Although these considered three diagnostic and therapeutic modalities for cervical dysplasia, the authors did not include cervical excision procedure histopathology. In addition, they examined agreement within one degree, which does not make clinical sense with the 2001 Bethesda System cervical cytology nomenclature (**Table 3, page 12**), which is a two tier system (**Refer to Appendix B**).

Massad, Collins, & Meyer (2001) performed a prospective study on 1842 women who were referredwith abnormal ctrology and assessed the agreement between repeat cytology, colposcopy, and colposcopic guided cervical punch biopsy after short follow up and observed agreement of 35.0% between Pap and cervical biopsy (k=0.20) and undercall of 31% and overcall of 35%. The authors did not ask for central review of cytology and or histopathology reports.

Agreement between cervical cytology, cervical biopsy histopathology, and cervical excision procedure histopathology

Three studies reported agreement between cervical cytology, cervical punch biopsy histopathology, and cervical excision procedure histopathology.

Heatley and Bury (1998) performed a prospective study in 107 women to assess the reliability cervical punch biopsy over cytology and also correlation between cytology, cervical punch biopsy and cone biopsy. The authors reported 63.0% percent agreement between colposcopic directed cervical biopsy and cone histopathology and 49.0% agreement between cytology and cone. The authors concluded that due to inter and intraobserver variability in grading of cytological and histopaythological findings, all tests and / or procedures are needed for management of cervical dysplasia.

Cetzin et al. (1998) performed a retrospective chart review on 280 women who had undergone cone biopsy and concluded that cytology and cervical biopsy histopathology doesnot predict final histopathology on cone biopsy and conization should be used to triage cervical dysplasia and performed for unsatisfactory colposcopy, discrepancy between cytology and colposcopy.

Ang et al. (1995) performed a retrospective study to assess the correlation between colposcopic guided cervical biopsy histopathology and Large Loop Excision Procedure (LETZ) histopathology in 242 patients. Exact percent agreement was noted in 67.0% of

LSIL and 79.0% of HSIL on cervical biopsy and 83.0% agreement within one grade was found on cervical biopsy histopathology and LETZ histopathology. Two (0.8%) women had microinvasive carcinoma which was missed by cervical biopsy. Because of the known complications associated with LETZ it was advised to use LETZ in selective cases.

Comparison between cervical cytology and colposcopy

Lyall and Duncan (1995) performed a retrospective review of 3,046 women cytology from single laboratory and histopathology from a single colposcopy clinic over six year period and noted that discrepancy between these two tests remained constant despite increase in total number throughout the study period. This study was a representative population and the authors concluded that persistent low grade abnormality on cytology should be referred for colposcopy for further evaluation. The authors did not assess the degree of agreement between these two tests.

Comparison between cervical cytology and cervical punch biopsy histopathology

Jones and Novis (1996) prospectively studied the diagnostic correlation between cervical cytology and cervical biopsy histopathology (the gold standard) in 22,439 specimen and reported 89.4% sensitivity and 64.8% specificity, and PPV of 89.0%. The authors reported that either cervical cytology or biopsy sampling error was the primary reason for the lack of correlation rather than due to interpretive errors. The authors recommended consideration of intradepartmental consultation and recuts in discrepancy cases with prior cytology diagnosis and regular monitoring of cervical cytology-histopathology correlation and correlation sharing between laboratories.

This study indicated poor correlation between cytology and cervical biopsy histopathology and since then cytopathologists and histopathologists have taken various steps in line with Jones & Novis' recommendations to improve tests interpretation.

Interobserver agreement studies for cytology and cervical punch biopsy histopathology

Several studies have assessed the agreement between observers for various modalities used in management of cervical dysplasia (below).

Table 5: Summary of Percent Agreement and Degree of Agreement Studies of Observers for Various Tests for Cervical Dysplasia Diagnosis and Treatment

Type of Study	Author / Date	Country	Size	Main Data Items	Main Results
Retrospective	Anderson et al. / 2004	UK	117	Cervical cytology and CPBx HPL between observers in two tier and three tier grading	Degree of AGT for intra-observer in Two tier system; k=0.57. Three tier system; k=0.39
Retrospective	Sideri et al. / 2004	Italy	100	Colposcopy (cervigrams) and LEEP HPL interpretation between colposcopists for several variables	Group k =0.69 for ATZ detection, and group k =0.48 for SCJ detection, k= 0.41 for HSIL, Overall poor AGT between studied parameters
Prospective	Stoler et al. / 2001	USA	4948, 2237, 535	Cervical cytology, CPBx HPL, and LEEP HPL interpretation between trained pathologists	Cytology; k=0.46, CPBx HPL; k=0.46, LEEP; k=0.49
Prospective	Kato et al. /1995	Spain and Colombia	1508/ 880	Cytology and CPBx HPL diagnosis, panel review of original diagnosis	Excellent inter-observer AGT between pathologists for invasive cancer, low for cervical dysplasia

Type of Study	Author / Date	Country	Size	Main Data Items	Main Results
Retrospective	Ismail et al. / 1989	UK	100	CPBx HPL between eight histopathologists	Overall percent AGT 0.36, (for invasive; 0.83, CIN III; 0.49, CIN II; 0.17, CIN I ;0.17)

Abbreviations: RCI= Reid colposcopic index; GC = general colposcopy; ATZ = abnormal transformation zone; SCJ = squamocolumar junction; CPBx = cervical punch biopsy; HPL = histopathology; AGT = Agreement

Anderson et al. (2004) performed a retrospective study to correlate cytological grading and biopsy histopathology using two and three tier systems to grade cervical dysplasia. In their study 117 women with conventional Pap smears and histopathology were included, and degree of agreement was calculated using kappa statistics. In both the two tier and the three tier systems the authors reported poor agreement between cytological grade with the histological categories, and moderate level of intra and interobserver agreement for cytological grading. For the three-tier system the interobserver kappa ranged from 0.30 to 0.60, and for the two-tier system the kappa varied from 0.18 to 0.38. In three-tier system most of the disagreement was of one grading category. The authors concluded that the inherent subjectivity in both cytology and histopathology interpretation may be expected less with two tier system. The authors also concluded that to avoid potential errors, there is a need for a proper training, monitoring and periodic assessment.

Sideri et al. (2004) analyzed 100 cervigrams (images of cervix obtained by colposcope) obtained by nine colposcopists during the colposcopic assessment of cervical dysplasia and correlated the findings with LEEP histopathology results using kappa statistics. The agreement for HSIL was fair (k=0.41) and low for LSIL. The authors concluded that some colposcopic features have clinical usefulness and good reproducibility and can justify a "see and treat" approach.

Stoler et al. (2001) assessed agreement between cytology, cervical biopsy histopathology, and LEEP histopathology from a large sample of data originally collected for an ongoing US multicentre clinical trial "AS-CUS LSIL Trial Study". The authors observed moderate interobserver reproducibility for both cytology and histopathological interpretation. Substantial agreement was noted for HSIL between colposcopic cervical biopsy and LEEP histopathology. This study information is important as the study was large, including over 7,700 subjects. The pathologists involved in the study were either gynecologic pathologists or highly academic pathologists with interest in research. This study underestimated the variability among pathologists (meaning, in most of the studies there is greater interobserver variation among cytopathologists and / or histopathologists). Stoler et al's findings cannot be expected in clinical practice as cytology is carried out in various laboratories and histopathological interpretations are carried out mainly by community pathologists. The study authors acknowledged limitations of k statistic in this study in terms of it being lower (compared to percent agreement) as it was carried out in highly selected referred population, compared to a screening population where cervical dysplasia is rare.

Kato et al. (1995) performed a case control study to evaluate inter-observer variations in diagnosis for cervical neoplasia and found overall reasonable agreement in cytology (n=1506) and biopsy histopathology (n=880). The authors observed excellent inter-observer percent agreement for invasive cancer in both cytology and cervical biopsy histopathology but poor agreement for cervical dysplasia.

Ismail et al. (1989) performed a study to evaluate inter-observer variations in cervical biopsy histopathological diagnosis and cytological grading of CIN and also found overall poor agreement (k=0.35). Agreement between observers was excellent for invasive cancer (k=0.83), moderately good for CIN 3 (k=0.49), and k for CIN 1 was 0.17, which is similar to the findings by (Kato et al, 1995). In both studies inter-observer agreement between cervical biopsy histopathology and final cervical excision procedure histopathology was not done. Based on poor reproducibility for lower grades of dysplasia, (Ismail et al,1989) suggested modification of the existing three tier grading system for cervical dysplasia and to consider a two tier system and also to incude a benign category of cervical epithelial changes. Kato et al. (1995) suggested review by a single histopathologist of cervical dysplasia instead of panel review.

Quality assurance studies in regards to the performance of colposcopists and pathologists

Benedet, Matistic & Bertrand (2004) carried out a quality assurance study in British Columbia to assess the degree of correlation between colposcopic impression, cytology, and cervical biopsy histopathology. The researchers found overall percent agreement between cytology and cervical biopsy in 79.4% of cases and between colposcopy and directed cervical biopsy (within one degree of each other) in 86.8% of cases. The authors also found that the performance scores of five out of 37 colposcopists were below the standard. Another quality assurance study involving simultaneous samples of non-correlating cervical cytology and biopsy done by (Dodd et al,1992) showed a significant number of false negative Pap smears due to sampling errors and a small proportion of interpretation errors within one degree of dysplasia.

Cervical Dysplasia Follow Up

There is no standard follow up protocol in Alberta and elsewhere in Canada after LEEP or cone biopsy for cervical dysplasia management even if LEEP or cone biopsy reveals a positive margin **(Figure 3, overleaf).** Protocols being used are not based on strong evidence. It appears that practices vary from institution to institution as well as between different colposcopists at the same institute (Detrich et al, 2002; Nelson, Duggan, & Nation, 2006).

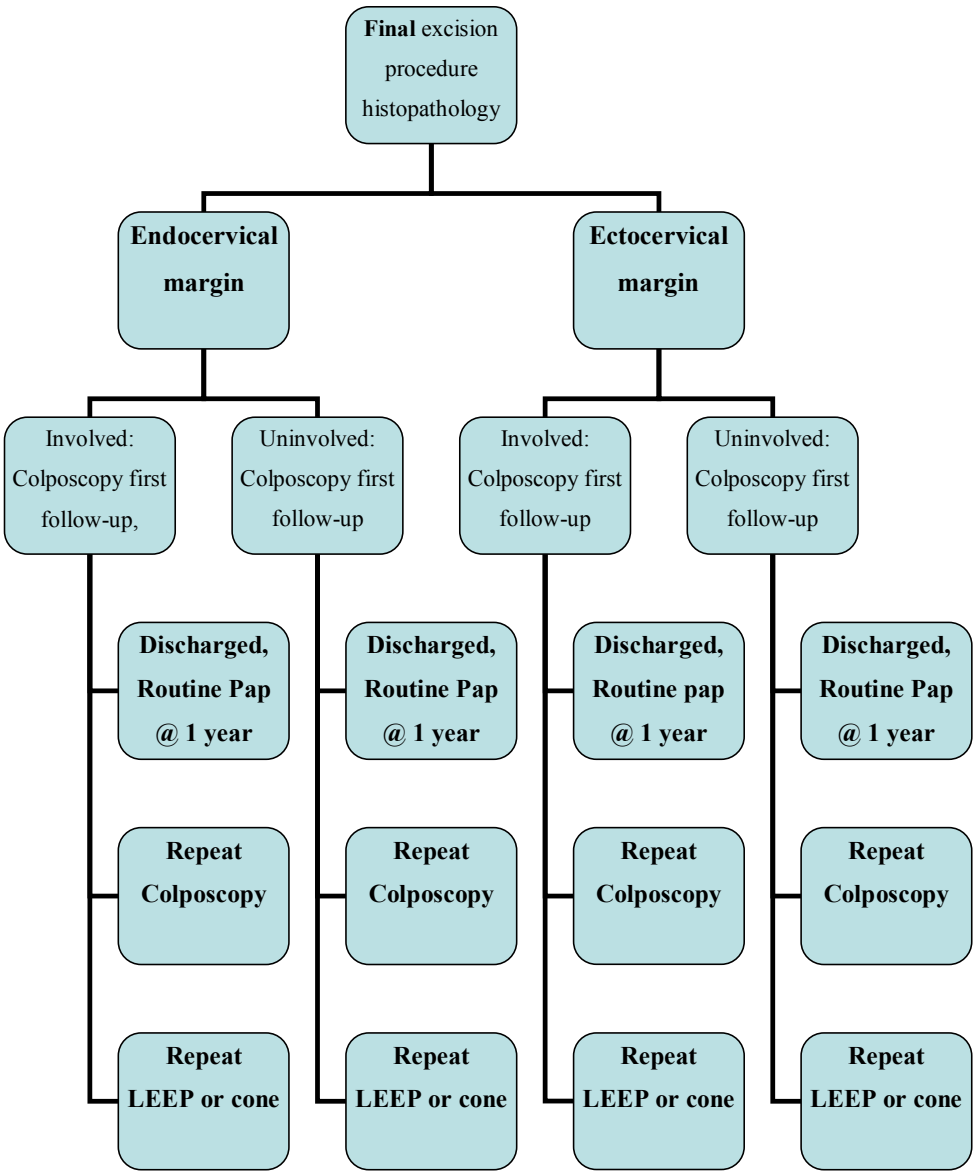


Figure 3: Flowchart of the Follow-up Protocol after Final Cervical Excision Procedure in Colposcopy Clinic

The various recommendations advised to women at the first follow up after final cervical excision procedure in colposcopy clinic is illustrated in **Figure 3, (page 45).**

Several authors have proposed different follow up protocols in terms of duration and types of recommendations based on their experience and study findings **(Table 6, below).** Following the table, studies are discussed in the order described in the table.

Table 6: Summary of Studies of Recommended Follow up After Cervical Excision Treatment for Cervical Dysplasia

Study Details	**Author / Date**	**Country**	**Size**	**Main Results**	**Proposed Follow up Recommendation**
Literature review	Bornstein et al. / 2004	Israel	Not applic -able	Involved cervical margin after final excision and the presence of HPV-DNA are associated with higher risks of disease recurrence and it should be considered during follow up of these women.	Initial follow up visit at 6 months after LEEP and should have colposcopy and cytology and every six months for 3 years with no residual disease and in women with residual disease follow up should be continued for 8 years.
Retrospective	Dietrich et al. / 2002	USA	298	Mean time to develop recurrent cervical dysplasia is 6-8 months not 3 months.	Initial follow up visit at 6 months after LEEP and should have colposcopy with screening cytology in women with residual disease.

Formatted Table

Study Details	Author / Date	Country	Size	Main Results	Proposed Follow up Recommendation
Prospective	Reich et al. / 2002	USA	390	In women with involved margin after 19 years of mean follow up, 306 (78.0%) CIN free, 84 (22.0%) had persistent (53) or recurrent (25) CIN and 5 women developed microinvasive and one invasive cancer stage 1B	Careful follow up in first year with colposcopy and Pap smear is adequate in women with involved margin after cold knife conisation. Repeat cone is not necessary.
Prospective	Reich et al. / 2001	USA	4417	In women with uninvolved margin after 18 years of mean follow up; 4402 (99.6%) remained free of CIN & 15 (0.4%) developed CIN II or CIN III, 2 (0.05%) developed preinvasive disease	Annual colposcopy and Pap smear is adequate in women with uninvolved margin after cold knife conisation
Retrospective	Gornall et al. /2000	UK	33	Two thirds of the invasive carcinoma were diagnosed in first 5 years and upto 94.0% diagnosed within 10 years of initial treatment	Follow up longer than 5 years in older women and those with incomplete excision of high grade sysplasia
Retrospective	Zaitoun et al. / 2000	UK	1,600	Residual pre-invasive disease, nine fold increases risk of invasive cancer	5 yr follow up in women with no residual disease. 10 yr follow up, in CIN III incompletely excised.

Formatted Table

Study Details	Author / Date	Location of study	Size	Main Results	Proposed Follow up Recommendation
Prospective	Dinh et al. / 1998	USA	74 /127	64.0% spontaneous regression rate of CIN after LEEP margin positive (HSIL in 82%)	Cytological follow up at 4 month intervals for 1 year and then 6 monthly in 2nd year is adequate. With five consecutive negative Paps, recommended annual Pap.
Retrospective	Soutter et al. / 1997	UK	2,116	Invasive cervical cancer 5.8 / 1000 women in 8 year follow up.	Suggested annual follow up at least 10 years after treatment.
Retrospective	Gardeil et al. 1997	UK	225	Increased risk of residual dysplasia with positive margin (16.5% in positive margin versus 1.9% in negative margin)	Pap alone is sufficient in follow up of women with negative margin.

Bornstein et al. (2004) after performing a metaanalysis, proposed a follow up protocol for women with HSIL who were treated with LEEP that included a Pap smear every six months for a period of three years if margins were clear. If the margins were positive then follow up would continue for eight years and then the patient would be referred to the family doctor for annual Pap smear. Another alternative recommended was to do human papilloma virus (HPV)-DNA testing in women with positive cervical margins because HPV-DNA is found in 96.0% of patients with recurrent CIN and testing is highly sensitive. Furthermore there is evidence that high risk HPV-DNA status six

months after LEEP excision is associated with the presence of recurrent or residual disease.

Dietrich et al. (2002) performed a retrospective review of follow up data of 298 women to assess the recurrence of cervical dysplasia and found that incomplete excision of cervical dysplasia increases the failure rate of LEEP. The authors recommended an initial follow up visit at six months after LEEP and it should include colposcopy with screening cytology in women with residual disease.

Reich et al. (2002) performed a prospective study of 5,386 women after cold knife conization for CIN 3 and followed them for a mean of 19 years, and observed 22.0% recurrence in women with involved margin. The authors also reported seven percent of women had invasive lesions. The authors concluded that the comparatively higher rate of recurrence noted in this study could be due to long term follow up as most comparable studies reported a mean follow up of six years. However two thirds of recurrence was diagnosed in first year of follow up so careful follow up is needed.

Reich et al. (2001) in their prospective follow up study of 4,417 women after cold knife conization for CIN 3 for mean of 18 years follow up, observed 0.4% recurrence in women with uninvolved margin. The authors concluded that cold knife conization is an appropriate treatment for CIN 3 and annual colposcopy and Pap smear is adequate for follow up in women with uninvolved margin.

Gornall et al. (2000) in UK performed a retrospective chart review of 33 women with cervical cancer and noted that 33.0% cases of invasive cancer post CIN treatment were detected after 5 years of follow-up. The authors concluded that residual cervical dysplasia (positive margin of the LEEP or cone specimen) increases the risk of subsequent invasive carcinoma by nine-fold compared to those with no evidence of residual disease.

Zaitoun et al. (2000) performed a retrospective study analyzing the follow-up data of 1600 women and concluded that a 10 year follow-up should be implemented for women with incomplete or equivocal CIN 3 excision.

Dinh et al. (1998) performed a prospective one year follow up study on 74 women out of 127 women who had involved margins after LEEP. The authors noted that 92.0 % of them had involved endocervical margin and only four% had iectocervical margin involved and noted 64.0% spontaneous regression on cervical cytology follow up or after repeat cone.

Soutter et al. (1997) analyzed 2116 women who were under observation eight years after treatment of CIN and found the cumulative rate of invasion was 5.8 per 1000 women. The risk of invasive cervical cancer among women with a history of CIN was five times greater than that of the general population.

Gardeil et al. (1997) performed a retrospective chart review of 225 women who had undergone LLETZ for severe cervical dysplasia and had been followed for mean of

two years. The endocervical margin was involved in 76 (34.9%) women. The authors observed increased risk of residual dysplasia in women with positive margin (16.5% in positive margin versus 1.9% in negative margin). The authors concluded that after complete excision of cervical dyaplasia Pap smear alone should be used for follow up. The presence of involved margin after LLETZ is one of the reasons for treatment failure of cervical dysplasia.

In summary, various studies have reported that women with HSIL involving the excision margin of a conization specimen, especially endocervical margin and post excision procedure endocervical sampling, are at higher risk of persistence of disease compared to women with clear margins (Moore, Higgins, & Laurentl, 1995; Kobak et al, 1995; Chang et al, 1996). Although margin involvement is not an independent risk factor for recurrence or persistence, other risk factors include age, larger lesion and HSIL (Kobak et al, 1995; Moore, Higgins, & Laurent, 1995). Cervical cytology has 64.0% sensitivity and it improves to 91.0% if combined with colposcopy at the cost of decreased in specificity from 95.0% to 88.0% (Soutter et al, 2006) and is used for follow up in some centers. Most recurrent or persistent cervical dysplasia is found in the first five years with the highest risk in the first year, although cases of invasive cancer have been reported up to 20 years after initial therapy. (ACOG practice bulletin, 2008).

Follow up for at least 20 years after LEEP to detect residual, recurrent, or persistent disease has been suggested (ACOG: Practice bulletin, 2005; Gornall et al,

2000). Repeat excision procedure can be offered although it is not recommended for the adolescent population because of associated risks of procedure.

The follow-up protocol after cervical dysplasia treatment of patients in CHR is described in **Figure 3, (page 45)** Although an important consideration in the management of cervical dysplasia, and one that requires considerable health care resources, follow-up is out of scope of the present thesis. Further, an assessment of long-term patient follow-up would not help to discuss the feasibility of the "see and treat" approach to the management of cervical dysplasia. It is in women unable or unwilling to attend for follow-up that the "see and treat" approach is most valuable. The literature highlighting the debate about the best protocol for follow-up demonstrates the importance of identifying the best and most consitent methods of initially managing cervical dysplasia to prevent further progression and identifying recurrence at the earliest.

Summary

There are many quality assurance measures in place which have greatly improved patient outcomes of abnormal cervical cytology. Previous studies in this area have mainly investigated the sensitivity and specificity of colposcopic impression, focusing on the agreement between colposcopic diagnosis and final excision histopathology or cytology, cervical biopsy histopathology, and colposcopic diagnosis reports. These studies did not include assessment of agreement between colposcopic impression, cervical punch biopsy histopathology and final excision biopsy histopathology. One of the possible reasons for not assessing the degree of agreement between these procedures could be the primary objectives of the studies themselves. These studies were not designed to study the feasibility of the "single visit see and treat" approach (Bigrigg et al, 1990; Luesley et al, 1990).

The studies which intended to examine the agreement between colposcopic impression, colposcopic directed punch biopsy histopathology, and conization, did not in fact look for the degree of agreement (k). The authors in these studies did not assess percent agreement between all three modalities (Boelter & Newman, 1975; Ngan et al, 1993).

It is important to look at the agreement between colposcopic impression and cervical punch biopsy histopathology as it will help in determining diagnostic accuracy of colposcopic impression, indirectly reflecting the colposcopic skills of the center. If

research shows significant agreement between colposcopic impression and final excision biopsy histopathology, then this will enable the future implementation of "single visit see and treat" practice for HSIL in high risk and poor compliance patient population (Bigrigg et al, 1990; Luesley et al, 1990). Such a clinic would eliminate the need for a preliminary cervical punch biopsy, and enable simultaneous histological diagnosis and treatment of premalignant cervical disease.

This study set out to fill this gap in the literature by assessing the agreement between the three important evaluation and treatment procedures: colposcopic impression, cervical punch biopsy histopathology, and final excision biopsy histopathology in those women who underwent final cervical excision procedure.

CHAPTER 3 RESEARCH QUESTIONS

Primary Research Question

In patients undergoing final cervical excision procedure for treatment of cervical dysplasia, what is the agreement between:

- Colposcopic impression and final excision biopsy histopathology
- Cervical punch biopsy histopathology or ECC and final excision biopsy histopathology
- Colposcopic impression and cervical punch biopsy histopathology or ECC

Secondary Research Question

In patients undergoing final cervical excision procedure for treatment of cervical dysplasia:

- What are the indications for final cervical excision procedures?

CHAPTER 4 RESEARCH METHOD

Introduction

Details of the study design are presented in this chapter, including the inclusion and exclusion criteria, sources of data and the data collection procedure, the data cleaning process, strategies used to deal with missing data, and data analyses. Definitions for terms used in the method are appended (**Appendix B**).

Study Design

This was a descriptive study, which involved review of the charts. It involved those women who underwent final cervical excision biopsy procedure (LEEP cone, LEEP biopsy, or cold knife cone biopsy) and no intervention was incorporated into the study (Creswell, 2003). The study was conducted retrospectively by reviewing charts of all eligible women who underwent final cervical excision biopsy procedure from January 2003 to December 2004 after having an abnormal colposcopic impression and an abnormal cervical punch biopsy histopathology or abnormal ECC histopathology (F**igure 1, page 10**).

Population Studied

This study was undertaken in the Calgary in the province of Alberta. Alberta, like the rest of Canada, has a universal health care plan in which all residents with a valid health card number are eligible to receive free health care service. The Women's Health Centre (WHC) Colposcopy Clinic and the Tom Baker Cancer Centre (TBCC) Colposcopy Clinic are the colposcopic referral centres for patients screened at various clinics operated by CHR in Southern Alberta **(**Refer to CHR map in **Appendix C).** At the time of the study, 15 gynecologists performed colposcopy in the WHC colposcopy clinic and three gynecologic oncologists in TBCC colposcopy clinic.

Subject Identification

The WHC colposcopy clinic monthly log book for cervical excision biopsy procedure was used to identify patients who had undergone this procedure. The weekly operative room list for TBCC was reviewed to identify patients who had undergone the same procedure.

Inclusion Criteria

- Women 18 years or older who underwent final cervical excision procedure (LEEP biopsy or LEEP cone, cold knife cone biopsy,).

Exclusion Criteria

- Invasive cervical cancer diagnosis on cervical punch biopsy
- Women having second cervical cone biopsy within 3 months of first cervical cone biopsy procedures at other colposcopic centre outside the CHR.

Details of Diagnostic Procedures

The colposcopic examination was performed using 3 to 5.0% acetic acid by either one of the 15 faculty colposcopists or by obstetrics and gynecology residents under direct faculty supervision at WHC. At TBCC the colposcopy was performed by residents under supervision of three gynecologic oncologists or by gynecologic oncologists themselves. Colposcopic impression was recorded on a standardized colposcopy form and reported as benign atypia, condyloma / human papilloma virus (HPV) changes, CIN 1, CIN 2, CIN 3, or low grade squamous intraepithelial lesion (LSIL), and high grade squamous intraepithelial lesion (HSIL). When a range was given or multiple findings were reported in the colposcopy chart, the highest grade (most severe finding) was recorded in the data collection form.

The colposcopic guided biopsy of the cervix was done with punch biopsy forceps after infiltrating the cervix at the site of abnormality with 2.0% xylocaine with 1:100,000 epinephrine and was sent in10% formalin for histopathological examination. For all

patients who had LEEP biopsy or LEEP cone done at the WHC colposcopy clinic, it was performed under local anesthesia. The cervix was infiltrated with 2% xylocaine with 1: 100,000 epinephrine at 3, 6, 9, and 12 o'clock position. At TBCC all cervical excision biopsy procedure was performed under general anesthesia and 2% xylocaine with 1: 000,000 epinephrine was also infiltrated in the cervix. The LEEP procedure was performed according to the technique described by Prendiville et al, (1989). A fine wire loop of appropriate size (1, 1.5, 2, or 2.5 cm diameter) powered by ERBE (ERBOTOM ICC 200) was used and either a switch on the handle or foot control for the current was used. The power output used was 50 to 62 W for cutting, coagulation, and blend. The pure cutting current was used to remove the specimen and then ball diathermy on pure-coagulation was used to fulgrate the base of the wound and to achieve haemostasis if required. In some cases Monsel's solution was also applied at the base of the wound for haemostasis. The specimen was sent in 10.0% formalin for histopathological examination. In majority (n = 901) of cases ECC was performed after final cervical excision procedure.

Data Collection and Management

Data Collection

A standardised data collection form was developed to collect all the information to describe the population and associated risk factors for cervical dysplasia and cervical cancer. The data was extracted manually from the charts included the women's age, parity,

smoking habits, menstrual history, and use of contraceptives, hormone replacement therapy use, history of previous abnormal Pap smear, referral Pap smear, and history of previous cervical excision biopsy procedure done. In addition, colposcopic diagnosis, cervical punch biopsy histopathology, ECC, LEEP biopsy histopathology, LEEP cone histopathology, cold knife cone histopathology, status of cone margin, advised follow up, and history of any complication after final cervical excision procedure was recorded on the data form (refer to **Appendix B** for study terms definition). The worst diagnosis was recorded from both the cervical punch biopsy report, ECC report, and from final cervical excision procedure histopathology report during data collection. The data collection form is included in **Appendix D**.

Main Data Items

The main data items were defined as follows:

- **Initial colposcopic impression:** finding defined as HSIL, LSIL, negative (no colposcopic abnormality), others (included condyloma, HPV changes, squamous metaplasia etc.), and invasive cervical cancer

- **Cervical punch biopsy histopathology:** finding defined as HSIL, LSIL, negative (no colposcopic abnormality), others (included condyloma, benign atypia, HPV changes, SIL unqualified, SIL unqualified favoring HSIL, or LSIL, Immature squamous metaplasia with or without atypia, mature squamous epithelium, acute

and chronic inflammation), adenocarcinoma in situ (AIS), and invasive cervical cancer.

- **ECC histopathology:** finding defined HSIL, LSIL, negative (no colposcopic abnormality), others (included condyloma, benign atypia, HPV changes, SIL unqualified, SIL unqualified favouring HSIL, or LSIL, Immature squamous metaplasia with or without atypia, mature squamous epithelium, acute and chronic inflammation), AIS, and invasive cervical cancer.

- **Final cervical excision procedure (LEEP cone, LEEP biopsy or cold-knife cone) histopathology:** finding defined HSIL, LSIL, negative (no colposcopic abnormality), others (included condyloma, benign atypia, and HPV changes, SIL unqualified, SIL unqualified favouring HSIL, or LSIL, Immature squamous metaplasia with or without atypia, mature squamous epithelium, microglandular hyperplasia, tubal metaplasia AIS, and invasive cervical cancer.

- **Final cervical excision procedure (final LEEP cone, LEEP biopsy or cold-knife cone) histopathology margins:** finding will be defined as involved (positive) or uninvolved (negative).

Data Management

The information was first recorded on paper data collection forms **(Appendix D)** and subsequently entered in a password protected database created in MS Access. To validate the correct data entry in the database, 15.0% of the records were double entered and reviewed by a second person. All the information was abstracted manually from the paper chart for WHC patients and electronic chart for TBCC patients. None of the histopathology reports were re-reviewed during the data collection process, although in some patients' charts, the histopathology consult report was present and it was recorded as the final histopathology findings.

Statistical Considerations:

Sample Size

The sample size calculation estimated that 960 charts would be required. Assuming that approximately 10% would have incomplete data, this sample would yield 860 cases for analysis. If similar proportions of abnormal findings were found between LEEP biopsy, LEEP cone, cold-knife cone histopathology and colposcopy, ECC and / or cervical punch biopsy for 56.0% of women (as found by Cetjin et al, 2004), the study would be able to state this with a 95.0% confidence interval of 54 to 58.0%. If 79.0% of women were found to have similar proportions of abnormal findings between LEEP

biopsy, LEEP cone, cold-knife cone histopathology and colposcopy and or ECC, cervical punch biopsy (as found by Benedet et al, 2004) the 95% confidence interval would be 78.0% to 80.0%. This sample size was believed to be adequate for the purposes of the study.

Data Cleaning

Of the 1006 reviewed charts, after excluding those with missing information, all three procedures (colposcopy, cervical punch biopsy and / or ECC, and final cervical excision procedure) findings were present in only 933 charts. Of the remaining 933 charts the charts with AIS, invasive carcinoma, and / or microinvasive carcinoma were again excluded and finally **917** charts were left for the data analysis **(Figure 4, overleaf).** SIL and SIL unqualified were part of "others" category during the data collection process. For the statistical analysis purpose SIL and SIL unqualified were removed from the others category of cervical punch biopsy and final cervical excision procedure and were added in LSIL category **(Figure 5, page 65).**

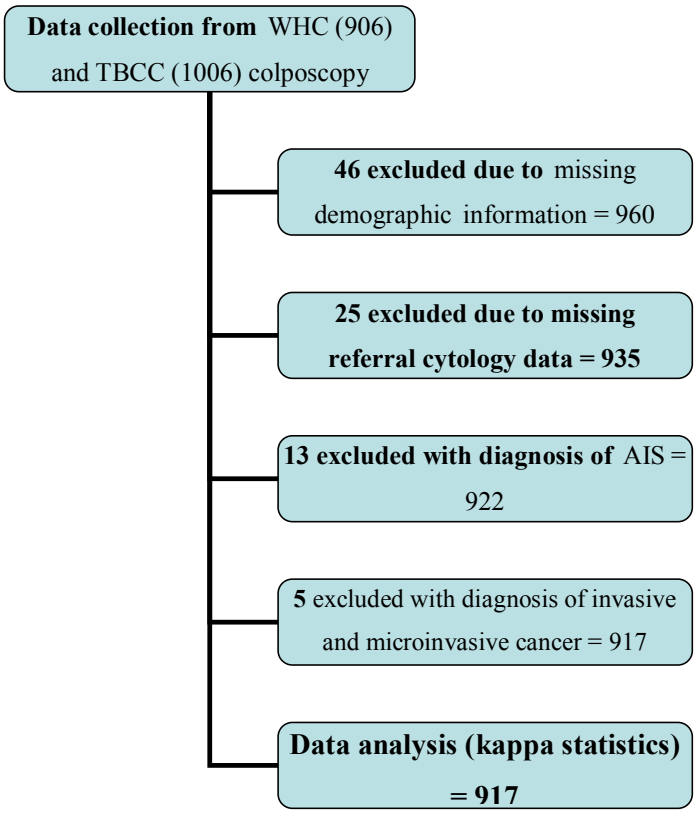
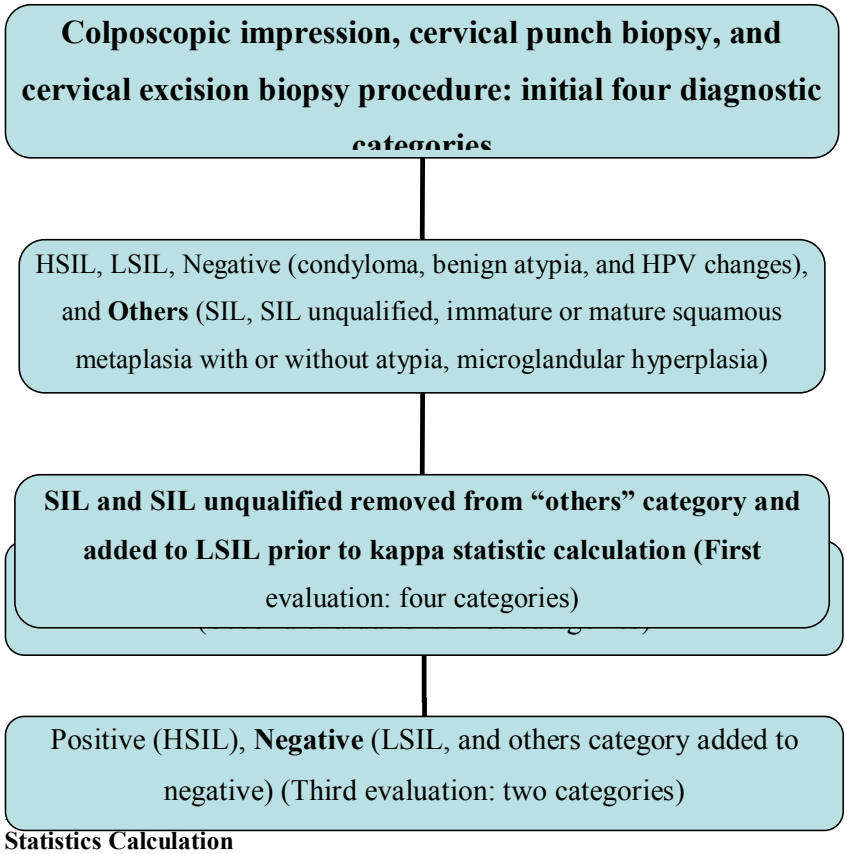


Figure 4: Flowchart of the Calculation of the Final Sample Size

Summary of final sample size (917) for final statistical analysis after exclusion of some diagnostic categories is shown in F**igure 4**.



Statistics Calculation

The details of various diagnostic categories and the process of reducing categories from four to two are demonstrated in F**igure 5**.

Statistical Analysis

The statistical analysis was performed using SAS version 8.0.Descriptive statistics were used to characterize study population demographics.

The analysis for the primary research questions involved assessment of the degree of agreementof diagnosis between colposcopic impression and cervical punch biopsy histopathology and / or ECC, and final cervical excision procedure histopathology finding. The degree of agreement between these data items was characterized by kappa statistic.

Kappa statistic:

Cohen's kappa is a robust statistical tool. It is indicated to assess the degree of agreement between more than two procedures, or procedures with more than two outcomes. It is an index of interobserver agreement that has been corrected for chance. Kappa also adjusts for disagreement between observers (procedures) and estimates degree of agreement after correcting for agreement by chance. Kappa is defined as the difference between observed and expected agreement expressed as a fraction of the maximum difference. The value of the kappa could range from -1.0 to 1.0, and value of zero indicates chance agreement only. The correlation was graded poor when the kappa value was less than 0.4, fair when the kappa value was between 0.4 to 0.6, good when the value ranged 0.6 to 0.8 and excellent if value was above 0.8 **(Table 7, page 67).** In this study three modalities (procedures) for cervical dysplasia diagnosis and / or treatment are considered as observers. Overall kappa statistic indicates the degree of interobserver agreement over and above that which would be expected by chance alone. The kappa is affected by prevalence and if disease prevalence is low, then despite high agreement kappa can be low. (Fleiss & Cohen, 1973 ; Landis & Kotch 1977; Gardner et al, 1989; DeVet et

al, 1990 ; Gordis, 1996; Feinstein & Cicchetti, 1998; Anderson et al, 2004; Sideri et al, 2004). The confidence intervals and the p-value for the kappa statistic were also calculated.

Table 7: Level of Agreement as Determined by the Value of Kappa Statistics (Landis & Koch 1977)

Kappa Statistics	Level of Agreement
0.00-0.40	Poor
0.41-0-60	Moderate
0.61-0.75	Good
0.76-0.99	Excellent
1.00	Perfect

T**able 7** describes the generally accepted definitions of the numerical kappa values. These values are used to compare the degree of agreement in this research.

.

Percent Agreement:

The overall percent agreement is not a statistical tool rather it is a descriptive method used to explain agreement between data. It does not adjust for degree of disagreement. The overall percent agreement requires creation of a two by two frequency table and it indicates the extent to which the two tests are in agreement. However, it fails to provide the nature of the disagreement (for example if one test consistently finds more positive result) and it also does not tell the extent to which the agreement improves on

chance alone (as considerable agreement would be expected by chance alone). The overall percent agreement however, does not differentiate between the agreement on the positives and agreement on the negatives. The overall percent agreement was estimated by creating 2 x 2 contingency tables as described by (DeVet et al 1990; Gordis L. 1996).

McNemar's Chi square test:

Pair wise McNemar test is applied to 2 x 2 contingency tables with two outcomes, with matched pairs of subjects, to determine whether the row and column marginal frequencies are equal ("marginal homogeneity"). The McNemar test is appropriately used in matched subjects, as well as in pairs of observations in individual subjects. However in this study, the tests were done sequentially in individual subjects, and this may impact on the independence if the test results of the earlier procedure was known at the time of the third procedure. The results of the first two procedures would have been known by the colposcopist and histopathologist performing and interpreting the final procedure. The final test was therefore not theoretically independent of the first two test results. In this study, despite the possible lack of independence, the tests were treated as being independent of each other, as would be the assumption in other examples of matched pairs of observations within individual cases.

The McNemar test looks at only the cases where there is disagreement and the elements of the main diagonal contribute no information. If the p-value of McNemar Chi square test calculated is less than 0.05 it signifies that the observers (colposcopic

impressions, cervical punch biopsy, and final cervical excision procedure in this research) are discordant (not homogeneous).

Statistical analyses:

In this study histopathological diagnosis of final cervical excision procedure histopathology was considered the gold standard measure to which different diagnostic categories of colposcopy impression and cervical punch biopsy histopathology were compared.

For the calculation of kappa statistic, cases with diagnoses of AIS, microinvasive cancer, and invasive cancer were not included, as these cases were very few in both cervical punch biopsy histopathology and final cervical excision procedure histopathology. It is not possible to have a diagnosis of AIS on colposcopic impression; therefore no cases of AIS were identified following this test **(Figure 4, page 64)**. Kappa statistic (k), was calculated for *four categories*: HSIL (included CIN 2-3), LSIL (CIN 1), others (included condyloma, benign atypia, and HPV changes), and negative. For final statistical analysis purposes, SIL and SIL unqualified were removed from the "others" category of cervical punch biopsy and final cervical excision procedure, and were added to the LSIL category. To assess if the degree of agreement between these three modalities changes, the main data items of initial colposcopic impression, cervical punch biopsy histopathology, and final cervical excision procedure histopathology were reduced to *two categories*: positive (HSIL), and negative (negative + others + LSIL), refer to **(Figure 5, page 65).**

The outcomes of the three types of procedures were defined as follows for statistica analysis:

- **Colposcopic impression and final cervical excision procedure histopathology:**
  - Four categories for kappa: HSIL, LSIL, Negative, and Others.
  - Two categories for kappa and McNemar: Positive, and Negative.
- **Colposcopic impression and cervical punch biopsy histopathology and or ECC:**
  - Four categories for kappa: HSIL, LSIL, Negative, and Others.
  - Two categories for kappa and McNemar: Positive, and Negative.
- **Cervical punch biopsy histopathology or ECC and final cervical excision biopsy histopathology:**
  - Four categories for kappa: HSIL, LSIL, Negative, and Others.
  - Two categories for kappa and McNemar: Positive, and Negative.

The colposcopic diagnosis was considered to be "overdiagnosed" if it was more advanced than the histopathological diagnosis from cervical punch biopsy and / or cervical excision specimen. The colposcopic diagnosis was considered to "underdiagnosed" if it was less advanced than that of histopathological diagnosis from punch biopsy and / or cervical excision specimen. Similarly the cervical punch biopsy diagnosis was considered to be "overdiagnosed" if it was more advanced than the colposcopic diagnosis and / or cervical excision histopathological diagnosis. The cervical punch biopsy diagnosis was considered to "underdiagnosed" if it was less advanced than the colposcopic diagnosis and / or cervical excision histopathological diagnosis. Similarly cervical excision

histopathological diagnosis was considered to be “overdiagnosed” if it was more advanced than the colposcopic diagnosis and / or cervical punch biopsy histopathological diagnosis. The cervical punch biopsy diagnosis was considered to “underdiagnosed” if it was less advanced than the colposcopic diagnosis and / or cervical punch biopsy histopathology diagnosis. (Refer to **Appendix B**– for study terms definition).

Pair wise McNemar test was performed for colposcopic impression, cervical punch biopsy histopathology and / or ECC, and final cervical excision procedure histopathology to test the discordance between these three procedures.

For the secondary research question, descriptive statistics were used to describe the indications for final cervical excision procedure. Continuous variables (e.g. age) were described in terms of their means and associated 95% confidence intervals.

In this study histopathological diagnosis of final cervical excision procedure histopathology was considered the gold standard measure to which different diagnostic categories of colposcopy impression and cervical punch biopsy histopathology were compared. Sensitivity, specificity, PPVs, and NPVs were calculated using standard formulae. To calculate sensitivity and specificity of colposcopic impression and cervical punch biopsy histopathology, final cervical excision procedure histopathology were used as gold standard.

Ethical Considerations

The research protocol was submitted to the University of Calgary, Conjoint Health Research Ethics Board (CHREB) for approval before the study began (refer to **Appendix E).** Ethics ID: E-20429, date of approval 2006/09/21).

Patient personal information was protected as follows:

- Each patient was given a unique identifier number that was used in the database to preserve anonymity.
- No identifiable data were recorded in the data collection form.
- Only the information that was needed to answer the research questions was obtained for each patient.

Other ethical considerations were as follows:

- There were no intervention in the study, and no direct or indirect contact with study subjects, so we obtained a waiver of consent based on the Tri-Council Policy recommendations (Canadian Institutes of Health Research, et al, 1998).
- The sample size for the study was 960, and therefore a waiver of consent was sought, on the grounds that it would be impractical to obtain consent from this large sample of women. In addition, many of the women may have moved since

2003-04, and tracing them would have been difficult, therefore feasibility would also be a problem.

- The findings of the study are presented in aggregate form and no individual patient would be identified in any way in results of the study.
- The paper data collection forms are securely stored in a locked office.

CHAPTER 5: RESULTS

Characteristics of Study Sample

The cohort for this study consisted of 1006 women (906 from WHC and 100 from the TBCC colposcopy clinic) who underwent a final cervical excision procedure for cervical dysplasia during the study period. Of those 89 women not included in the final data analysis, 46 were excluded because of missing demographic information, 25 excluded due to missing referral cytology data, 13 were excluded with the diagnosis of AIS, and five were excluded with the diagnosis of microinvasive cancer, and invasive cancer **(Figure 4, page 64).** The demographic characteristics of the sample population (n= 917) are displayed in **(Table 8, overleaf).**

Table 8: Study Cohort Demographics

Patients Characteristics (N =917)	Number (%) or mean, SD, range
Age in years (mean, SD, range)	32.2, 10.5, 16 to 80
Gravidity / Parity	
Nulligravida	373 (40.7)
Nulliparous	504 (55.0)
History of smoking	
No	580 (63.2)
Yes	327 (35.7)
Unknown / missing	9 /1(1.1)
Contraception use	
None	183 (20.0)
OCP	381 (41.5)
Others	340 (37.1)
Unknown / missing	11/2 (1.4)
Menopausal	
No	851 (92.8)
Yes	57 (6.2)
Unknown / missing	3/6 (1.0)
HRT use	
No	901 (98.2)
Yes	8 (0.9)
Unknown / missing	6/2 (0.9)

The mean age of patients was 32.2 years (range 16-80), with 64.2% of women between the ages 25 to 45 yrs. Of the 917 women included, 373 (40.7%) patients were nulligravida and 218 (23.8%) had been pregnant once. Mean parity was 1.0 (range 0-9). Of 917 women, 504 (55.0%) women were nulliparous, and 153 (16.9%) were primiparous. Of 917 women, 580 (63.2%) were nonsmokers, and 327 (35.7%) were current or former smokers. The oral contraceptive was used by 381 (41.5%), and 340 (37.1%) women used other forms of contraception, including vasectomy, tubal ligation, barrier methods, Depo-Provera, intrauterine contraceptive device (IUD), and rhythm method (**Table 8, page 76).**

Table 9: Referral Pap for Initial Colposcopy

Referral Pap Smear	Number (%)
AGC	18 (2.0)
ASC-H	42 (4.6)
ASC-US	65 (7.1)
AIS	2 (0.2)
HSIL	494 (53.8)
LSIL	263 (28.7)
Missing	33 (3.6)
Total	**917 (100.0)**

HSIL accounted for 494 (53.8%), LSIL for 263 (28.7%), and ASC-US accounted for 65 (7.1%) of referral Pap smears in those wopmen with cervical dysplasia **(Table 9, page 77).**

The mean interval between initial colposcopic assessment and final cervical excision procedure (the assessment treatment interval) visit was 67.9 days (ranged from zero to 731 days).

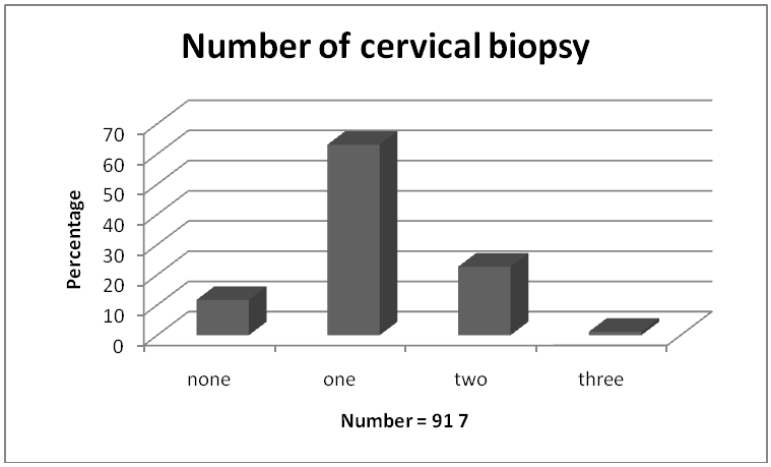


Figure 6: Number of Cervical Biopsies

Of the 917 women, cervical punch biopsy was not performed in 107 (11.7 %) women. One cervical punch biopsy was performed in 579 (63.1 %) women, 218 (23.8%) women had two biopsies, only 11 (1.2 %) had three biopsies performed at the same visit and information was missing in two (0.2%) women **(Figure 6**).

Test Results for the Study Cohort

Table 10: Test Results of Study Cohort

Diagnosis	Colposcopic Impression: N (column %)	Cervical Punch Biopsy / ECC Histopathology: N (column %)	Final Cervical Excision Procedure Histopathology: N (column %)
HSIL	355 (38.7)	594 (64.8)	653 (71.1)
LSIL	388 (42.3)	109 (11.9)	186 (20.3)
NEG	105 (11.5)	36 (3.9)	24 (2.6)
Others	69 (7.5)	178 (19.4)	54 (5.9)
Total	**917 (100.0)**	**917 (100.0)**	**917 (100.0)**

Formatted Table

The colposcopic impression was negative in 105 (11.5%) women, others (HPV changes, squamous metaplasia, condylomatous changes) in 69 (7.5%), and HSIL in 355 (38.7%) women **(Table 10).** An ECC was done in 107 (11.7%) women, 105 of those had negative colposcopic impression and cervical punch biopsy was not performed, according to the CHR colposcopic clinic guideline. An ECC histopathology (n=105) finding was recorded instead of cervical punch biopsy histopathology in these women.

Colposcopic directed cervical biopsies and /or ECC reported no pathological abnormality (negative) in 36 (3.9%), HSIL in 594 (64.8%,) and others (included condyloma, benign atypia, HPV changes, SIL unqualified, SIL unqualified favouring

HSIL, or LSIL, immature squamous metaplasia with or without atypia, mature squamous epithelium, acute and chronic inflammation) in 178 (19.4%) women **(Table 10, page 79).**

Final excision procedure histopathology reported no pathological abnormality (negative) in 24 (2.6%), HSIL in 653 (71.1%), and others (included condyloma, benign atypia, and HPV changes, SIL unqualified, SIL unqualified favouring HSIL, or LSIL, immature squamous metaplasia with or without atypia, mature squamous epithelium, microglandular hyperplasia, tubal metaplasia), in 54 (5.9%) women **(Table 10, page 79).**

Table 11: Endocervical and Ectocervical Margin Histopathology of Final Cervical Excision Procedure

Diagnosis	Endocervical Margin N (Column %)	Ectocervical Margin N (Column %)
HSIL	127 (13.8)	58 (6.3)
LSIL	32 (3.5)	47 (5.1)
SIL	13 (1.4)	10 (1.1)
Not reported	64 (7.0)	69 (7.5)
Missing	41 (4.5)	38 (4.1)
Uninvolved	640 (69.8)	695 (75.8)
Total	**917 (100.0)**	**917 (100.0)**

The endocervical margin of the final excision procedure histopathology was reported as uninvolved in 640 (69.8%), HSIL in 127 (13.8%), and as SIL in 13 (1.4%). The ectocervical margin of the final excision procedure histopathology was reported as uninvolved in 695 (75.8%), HSIL in 58 (6.3%), and as SIL in 10 (1.1%) women **(Table 11, page 80).**

Table 12: Degree of Involvement of the Endocervical Gland in Final Cervical Excision Procedure

Cervical Glandular Involvement	Number (%)
Deep	69 (7.5)
Intermediate	143 (15.6)
Superficial	235 (25.6)
Not reported	301 (32.8)
None	133 (14.5)
Missing	36 (3.9)
Total	**917 (100.0)**

The involvement of the endocervical gland was absent in 133 (14.5%), deep involvement was present in 69 (7.5%), and was not reported in 301 (32.8%) women **(Table 12).**

Table 13: Post Final Cervical Excision Procedure ECC Histopathology

Diagnosis	Number (%)
HSIL	39 (4.3)
LSIL	17 (1.8)
Others	106 (11.6)
No pathological abnormality	739 (80.6)
Missing	16 (1.7)
Total	**917 (100.0)**

The post final excisional procedure endocervical curettage histopathology reported HSIL in only 39 (4.3%) and no pathological abnormality (negative) in 739 (80.6%), women **(Table 13).**

Table 14: Comparison of Involved Endocervical Margin and Post Final Excision Procedure ECC Histopathology

Involved Endocervical Margin	Post LEEP ECC Histopathology (number / total %)				
	HSIL	**LSIL**	**Others**	**No pathological abnormality**	**Total**
HSIL	27 (16.2)	3 (1.8)	20 (12.0)	74 (44.2)	124 (74.2)
LSIL	1 (0.6)	4 (2.4)	21 (12.6)	6 (3.6)	32 (19.2)
Others (SIL)	1 (0.6)	0	2 (1.2)	8 (4.8)	11(6.6)
Total	**29 (17.4)**	**7 (4.2)**	**43 (25.7)**	**88 (52.7)**	**167 (100)**

172 women had some degree of involvement of the endocervical margin. Of those, 167 also had a reported post final excisional procedure ECC histopathology. Among the 167 patients for whom both reports were available, 124/167 (74.2%) had HSIL reported on final excisional procedure histopathology, while only 27/167 (16.2%) had HSIL reported on post final excisional procedure ECC histopathology **(Table 14, page 82)**.

Assessment of the degree of agreement of three diagnostic and / or therapeutic procedures

Colposcopic impression by cervical punch biopsy histopathology or ECC

Table 15a: Agreement between Colposcopic Impression and Cervical Punch Biopsy Histopathology

Colposcopic Impression	Cervical Punch Biopsy Histopathology, n (Total %)				
	HSIL	LSIL	Others	Negative	Total
HSIL	252 (27.5)	50 (5.5)	41 (4.5)	12 (1.3)	355 (38.7)
LSIL	292 (31.8)	42 (4.6)	38 (4.1)	16 (1.7)	388 (42.3)
Others	41 (4.5)	10 (1.1)	15 (1.6)	3 (0.3)	69 (7.5)
Negative	9 (1.0)	7 (0.8)	84 (9.2)	5 (0.6)	105 (11.5)
Total	**594 (64.8)**	**109 (11.9)**	**178 (19.4)**	**36 (3.9)**	**917 (100.0)**

- **Kappa statistic: 0.03 (-0.00-0.06)**
- **Kappa: p-value = <0.0001**

Table 15b: Agreement between Colposcopic Impression and Cervical Punch Biopsy Histopathology

Colposcopic Impression	Cervical Punch Biopsy histopathology N (Row %)		
	Positive	Negative	Total
Positive	252 (27.4)	103 (11.2)	355 (38.7)
Negative	342 (37.3)	220 (24.0)	562 (61.3)
Total	**594 (64.7)**	**323 (35.2)**	**917 (100.0)**

- **Kappa statistic: 0.09 (0.036-0.14)**
- **Kappa: p-value = <0.0001**
- PPV= 252 / 355*100%= 70.9%
- NPV=220 / 562*100%= 39.1%
- Percent Agreement = (252 + 220) / 917*100% = 51.5%
- Percent disagreement = (103 +342) / 917*100% = 48.5%
- False Positive Rate (Overcall) = (103 / 355) *100% = 29.0%
- False Negative Rate (Undercall) = (342 / 562) *100% = 60.8%
- **McNemar's p-value = <0.0001**

In **Table 15a (page 84)**, the degree of agreement between colposcopic impression and cervical punch biopsy histopathology was examined for all four diagnostic categories, the overall kappa value was 0.03and it represented poor agreement. When the degree of agreement was compared for HSIL only, the kappa value was 0.09 which represented poor agreement. The sensitivity and specificity was not calculated **(Table 15b, page 84).** [2]

Out of 355 women with positive colposcopic impression, it was falsely positive in 103 (103 / 355 *100% = 29.0 %) women **(Table 15b, page 84)** The NPV of colposcopic impression for HSIL was 39.1%. The p-value of McNemar Chi square test was < 0.0001, which indicated discordance between observers (colposcopic impressions, cervical punch biopsy, and final cervical excision procedure in this research).

---

[2] Sensitivity and specificity was not calculated for this category as there was no gold standard

Colposcopic impression by final cervical excision biopsy histopathology

Table 16a: Agreement between Colposcopic Impression and Final Cervical Excision Procedure Histopathology

Colposcopic Impression	Final Cervical Excision Procedure (LEEP) Histopathology, n (Total %)				
	HSIL	**LSIL**	**Others**	**Negative**	**Total**
HSIL	281 (30.6)	54 (5.9)	14 (1.5)	6 (0.7)	355 (38.7)
LSIL	284 (30.9)	79 (8.6)	17 (1.9)	8 (0.9)	388 (42.3)
Others	41 (4.5)	17 (1.9)	8 (0.9)	3 (0.3)	69 (7.5)
Negative	47 (5.1)	36 (3.9)	15 (1.6)	7 (0.8)	105 (11.5)
Total	**653 (71.2)**	**186 (20.3)**	**54 (5.9)**	**24 (2.6)**	**917 (100.0)**

- **Kappa statistic: 0.06 (0.02-0.10)**
- **Kappa: p-value = <0.0001**

Table 16b: Agreement between Colposcopic Impression and Final Cervical Excision Procedure Histopathology

Colposcopic Impression	Final Cervical Excision Procedure Histopathology N (Row %)		
	Positive	**Negative**	**Total**
Positive	281 (30.6)	74 (8.1)	355 (38.7)
Negative	372 (40.6)	190 (20.7)	562 (61.3)
Total	**653 (71.2)**	**264 (28.8)**	**917 (100.0)**

- **Kappa statistic*: 0.11 (0.06-0.163)***
- ***Kappa: p-value* = <0.001**

- Sensitivity=281/653*100%=43.0%
- Specificity=190 / 264*100%= 71.9%
- PPV=281 / 355*100%= 79.2%
- NPV=190 / 562*100%= 33.8%
- Percent Agreement = (281 +190) / 917*100% = 51.3%
- Percent disagreement = (74+372) / 917*100% = 48.7%
- False Positive Rate (Overcall) = (74 /355) *100% = 20.8%
- False Negative Rate (Undercall) = (372 / 562) *100% = 66.2%
- **McNemar's p-value = <0.0001**

In **Table 16a (page 86)**, the degree of agreement between colposcopic impression diagnosis and final cervical excision biopsy histopathology was compared for all four diagnostic categories, the overall kappa value was 0.06 and it represented poor agreement. When the degree of agreement was compared for HSIL only, the kappa value was 0.11 which still represented poor agreement **(Table 16b, page 86).**

Out of 355 women with positive colposcopic impression it was falsely positive in 74 (74 / 100 / 355 *100% = 20.8%) women **(Table 16b, page 86)** The NPV of colposcopic impression for HSIL was 33.8% when negative was defined as all lesions except HSIL. The p-value of McNemar Chi square test was < 0.0001, which affirmed that observers (colposcopic impressions, cervical punch biopsy, and final cervical excision procedure in this research) in this study are discordant.

Cervical punch biopsy histopathology and / or ECC by final excision biopsy histopathology

Table 17a: Agreement between Cervical Punch Biopsy and Final Cervical Excision Procedure Histopathology

Cervical Punch Biopsy	Final Cervical Excision Procedure Histopathology N (Row %)				
	HSIL	**LSIL**	**Others**	**Negative**	**Total**
HSIL	477 (52.0)	82 (8.9)	21 (2.3)	0 (0.0)	580 (63.2)
LSIL	63 (6.9)	38 (4.1)	7 (0.8)	9 (1.0)	117 (12.8)
Others	91(9.9)	55 (6.0)	23 (2.5)	1 (0.1)	170 (18.5)
Negative	22 (2.4)	11(1.2)	3 (0.3)	14 (1.5)	50 (5.5)
Total	**653 (71.2)**	**186 (20.3)**	**54 (5.9)**	**24(2.6)**	**917 (100.0)**

- **Kappa statistic: 0.17 (0.13-0.22)**
- **Kappa: p-value = <0.0001**

Table 17b: Agreement between Cervical Punch Biopsy and Final Cervical Excision Procedure Histopathology

Cervical Punch Biopsy	Final Cervical Excision Procedure Histopathology N (Row %)		
	Positive	**Negative**	**Total**
Positive	477 (52.0)	117 (12.8)	594 (64.8)
Negative	176 (19.2)	147 (16.0)	323 (35.2)
Total	**653 (71.2)**	**264 (28.8)**	**917 (100.0)**

- **Kappa statistic: 0.26 (0.20 -0.33)**
- **Kappa: p-value = <0.0001**
- Sensitivity= 477 / 653*100% = 73.0%
- Specificity= 161 /264*100%= 61.0%
- PPV= 477 / 580*100%= 81.1%
- NPV= 161 / 337*100%= 47.7%
- Percent Agreement = 477 + 161 / 917*100% = 69.5%
- Percent disagreement = 103 +176 / 917 *100% = 30.5%
- False Positive Rate (Overcall) = (103 / 580) *100% = 17.7%
- False Negative Rate (Undercall) = (176 / 337) *100% = 52.2%
- **McNemar's p-value = <0.0001**

In T**able 17a (page 88)**, the degree of agreement between cervical punch biopsy histopathology was compared with final cervical excisional biopsy histopathology for all four diagnostic categories, the overall kappa value was 0.17 and it represented poor agreement. When the degree of agreement was compared for HSIL, the kappa value was 0.26, which still represented poor agreement **(Table 17b, page 88).**

Out of 580 women with positive cervical punch biopsy, It was falsely positive in 103 (103 / 580 *100% = 17.7%) women **(Table 17b, page 88**) The NPV of cervical punch biopsy for HSIL was 47.7%, when negative was defined as all lesions except HSIL. The p-value of McNemar Chi square test was 0.0006, which affirmed that observers

(colposcopic impressions, cervical punch biopsy, and final cervical excision procedure in this research) in this study are discordant.

CHAPTER 6: DISCUSSION

Overview of the Discussion

The discussion is presented in four broad sections. First, an overview of the findings and clinical implications for clinical practice are presented and the results in various categories are compared to the available literature. Second, the study's strengths and limitations including its validity, bias, methodological issues, and the study design are assessed. Third, the appropriateness of the statistics and other tools used is assessed. Lastly recommendations and future research ideas are discussed.

Overview of the Findings and Clinical Implications

The research for this thesis set out to examine the agreement between three diagnostic and / or treatment modalities; colposcopic impression, cervical punch biopsy histopathology, and final excision biopsy histopathology in those women who underwent final cervical excision procedure for the treatment of cervical dysplasia. This research was also designed to examine the indications for cervical excision procedure in women with cervical dysplasia.

The clinical implications of this study are to add arguments to the debate about whether it would be possible to eliminate the need for colposcopic guided cervical punch biopsy thus making a “see and treat single visit” practice approach feasible, in which simultaneous same visit diagnosis and treatment of cervical dysplasia could be conducted, without compromising quality of care.

Agreement between colposcopic impression and cervical punch biopsy histopathology in comparison to other published studies

The degree of agreement between these two procedures in this study is lower than those reported in several earlier studies. Exact degree of agreement between colposcopic impression and cervical punch biopsy histopathology was poor (k = 0.03), it did not change much and remained poor (k = 0.09) when the result was allocated to the two categories of positive and negative (**Table 15b**). Other authors have reported slightly better degree of agreement (k). Massad & Collins (2003) observed k of 0.20, (Benedet, Matistic, & Bertrand, 2004) reported k of 0.36, and (Baum et al, 2006) reported k of 0.19.

The overall percent agreement was noted to be 51.5%, which is also lower than those reported in other studies. Although some of the studies have reported lower percent agreement. Korkolopoulou et al. (1992) found 45.1% agreement. Ngan et al. (1993) reported 76.7% agreement, (Massad & Collins, 2003) observed 75.0%, and (Benedet, Matistic, & Bertrand, 2004) reported 86.8%, agreement, which is higher than this study.

Not all authors have examined the degree of agreement (k). The percent agreement is not a statistical tool and it does not adjust for disagreement so it is expected to be higher than kappa and it does not signify that there is good to excellent degree of agreement between different procedures.

Agreement between colposcopic impression and final cervical excision procedure histopathology in comparison to other published studies

The lack of degree of agreement between these two procedures observed in this study confirms that reported in other studies. The exact degree of agreement between colposcopic impression and final cervical excision procedure histopathology was found to be poor (k = 0.03) and it changed slightly (k = 0.11) when the result were reduced to two categories of positive and negative (**Table 16b**). Higgins et al. (1994) reported k of 0.09 and (Massad et al, 1996) reported k of 0.32.

The overall percent agreement for HSIL compared to all other categories was 51.3% which is lower than those reported in other studies. Although some of the studies have reported lower percent agreement. Ngan et al. (1993) observed 74.5% agreement, (Higgins et al, 1994) reported 57.0%, and (Heatley & Bury, 1998) reported 63.0% agreement which is similar to this study. Denny et al. (1995) observed 82.0% agreement, (Ferris et al, 1996), reported 82.0%, and (Ihonor et al, 1999) reported 83.0% agreement.

All these studies reporting higher agreement were carried out in comparatively smaller sample (n = 48 to 210) and the authors analysed exact and / or percent agreement within one degree but did not examine degree of agreement (k). In majority of these studies either the colposcopy was done by experienced colposcopists and / or pathology was reviewed by either a single pathologist or same group of experienced pathologists.

The percent agreement being a descriptive way to explain agreement does not account for existing disagreement which is adjusted in kappa statistics. If it is high, does not necessarily mean good to excellent agreement between different procedures.

Agreement between cervical punch biopsy and final cervical excision procedure histopathology in comparison to other published studies

The degree of agreement between these two procedures in this study is similar to that reported in several earlier studies. The exact degree of agreement between cervical punch biopsy and final cervical excision procedure histopathology was poor (k = 0.17) and it changed only slightly (k = 0.26), even after allocating the results to two categories of negative and positive (**Table 17b**). Higgins et al. (1994) observed k of 0.29, Massad et al. (1996) reported k of 0.34, (Baldauf et al, 1997) observed k of 0.20, (Ihonor et al, 1999) observed k of 0.20, and (Boonlikit et al, 2006) reported k of 0. 24 for cervical punch biopsy and LLETZ. Barker et al. (2002) reported k of 0.73 (n= 139) when compared to within one degree and k of 0.23 with perfect agreement.

The overall percent agreement was 69.5% for HSIL compared to all other categories which is lower than those reported in other studies. Although some of the studies have reported lower percent agreement. Yarnoz et al. (1988) noted 68.0% agreement between cervical punch biopsy and LEEP. Chappatte et al. (1991) reported 42.0% agreement, (Higgins et al, 1994) reported 57.0%, (Cetzin et al, 1998) found 40.0% agreement, (Heatley and Bury, 1998) observed 63.0%, and Ihonor et al. (1999) reported 61.0% agreement. These authors reported excellent percent agreement within one degree and of moderate degree exact percent agreement. Massad and Collins (2003) noted 75.0% agreement within one degree. Costa et al. (2003) noted in women with CIN III on cervical

biopsy agreement was 85.0% for HSIL, and 72.4% for LSIL. Baldauf et al. (1997) noted overall 89.6% agreement and 95.8% agreement for HSIL, (Guensekera et al, 1990) reported 93.0% agreement, (Barker et al, 2001) observed 84% agreement within one degree, and Barker et al. (2002) observed 81.0% agreement within one degree.

In most of these studies either the colposcopy was done by experienced colposcopists and / or pathology was reviewed by same group of experienced pathologists. When the percent agreement is compared between observers it does not correct for agreement by chance, which results in higher agreement compared to kappa.

Explanation of poor degree of agreement between the procedures

In the published literature the majority of studies have reported percent agreement and few of them also reported the degree of agreement (kappa statistic) between procedures (diagnostic and /or therapeutic). The percent agreement reported is in higher range when one degree of variation was considered compared to lower exact percent agreement (Benedet et al, 1991; Costa et al, 2003; Massad & Collins, 2003; Sideri et al, 2004). The agreement within one degree means that agreement between two tests or procedures is reported between first and third diagnostic category if there are more than two diagnostic categories. Exact or perfect agreement means that agreement is analyzed and reported within first and second diagnostic category out of three categories. The agreement within one degree is possible in the three tier system where cervical dysplasia is classified in three categories ((CIN I, CIN II, and CIN III)). The two tier system has only two diagnostic categories (HSIL and LSIL) for cervical dysplasia. In studies which have reported kappa statistic, the degree of agreement is in poor to fair range (Massad, Collins, & Meyer, 2001; Massad & Collins, 2003; Benedet et al, 2004; Boonlikit et al, 2006; Mousavi et al, 2007).

The current study showed poor exact degree of agreement on the studied diagnostic and / or therapeutic procedures. None of the 'k' values observed was higher than 0.26 (poor as defined by Landis & Koch, 1977). Due to inherent interobserver discrepancies between pathologists, agreement to within one degree had been considered

an appropriate measure in the three tier system. The agreement within one degree cannot be considered in a two tier system of histopathology reporting of cervical dysplasia. The clinical diagnosis and management guidelines recommend treatment of HSIL, while LSIL is not treated until it has persisted for two years or more (Wright et al, 2007). In the two tier system, if agreement is analysed within one degree, the differentiation between LSIL and HSIL would be lost, which would not be clinically relevent or appropriate (Ismail et al, 1989; Chappatte et al, 1991).

Lack of agreement between different diagnostic procedures could be due to inter and intraobserver variability in reporting the grade of the lesion, which has been well described. The variability is less for more severe lesions (Ismail et al, 1989; Chappatte et al, 1991; Wright et al, 2002; Soto-Wright et al, 2005). As colposcopic evaluation is a visual technique affected by observer subjectivity, it has low specificity (48.0% to 54.8%), and its accuracy varies according to the skill and experience of the colposcopists (Mariamma et al, 1991; Hopman et al, 1995; Mitchell et al, 1998; Sideri et al, 2004; Gage et al, 2006; Jeronimo & Schiffman, 2006). Barker et al. (2001) assessed the interval between cervical biopsy and LEEP, and found that even delay greater than 12 weeks had no effect in agreement between cervical biopsy and LLETZ histopathology. It is known that rate of progression of CIN can range from months to decades. The authors concluded that an average interval of 10 weeks between colposcopy referral and final excision should not change the cervical pathologic severity. The authors suggested that baseline errors inherent in testing schemes (that is, differences in time between colposcopy and other procedures differs in different clinics, resulting in significant differences in time from

initial colopscopy to final cervical excision), of cervical biopsy followed by cervical excision, may also account for this lack of agreement. These errors could be regression or progression of cervical dysplasia depending upon the severity of lesion.

As explained earlier the overall percent agreement is not a statistical tool and does not take in account either the considerable agreement that would be expected by chance alone or disagreement, and overstates the agreement between tests. This is reflected in this study results (better percent agreement than degree of agreement based on kappa statistic) as well as in most of the reported studies.

For all of the paired comparisons between the findings of each of the three procedures, the kappa values indicate poor agreement. The results for the McNemar's Chi square tests' p–values are less than 0.05. These results indicate that the procedures are discordant. Therefore the kappa and McNemar test results suggest that diagnoses among the three diagnostic and / or therapeutic procedures are not influenced by each other in this study. We assumed independence between the three diagnostic procedures even though the findings of the first two procedures (colposcopic impression, cervical punch biopsy histopathology) were known to the colposcopist at the time of the third procedure (final cervical excision procedure). The McNemar and kappa findings indicate that the outcome of the third procedure was not influenced by the findings of the previous procedures. This suggests that the assumption of independence among the three procedures was appropriate in this study.

The interpretation of discordance between procedure results could be that the severity of the lesions under investigation have truly changed between tests, either by improving as a result of lesions being completely excised during the procedure or by regression over time, or else by worsening as a result of disease progression. Alternatively, the discordance between procedure results could be as a consequence of the subjectivity, inter and intraobserver variation and unreliability of the procedures.

Description of undercall and overcall in these procedures

This study observed 60.8% undercall and 29.0 % overcall for colposcopy compared to cervical biopsy for HSIL, which is higher than percentage of undercall and overcall reported in several other studies. (Higgins et al, 1994; Cetzin et al, 1998; Ferris et al, 1998; Ihonor et al, 1999; Howe & Vincenti, 2001; Boonlikit et al, 2006).

This study found 52.2% undercall and 17.7% overcall for cervical biopsy compared to cervical excision procedure**,** which is higher than those reported in some studies. However some studies have observed lower undercall rate. Higgins et al. (1994) reported 23% undercall and 12% overcall. Chappatte et al. (1991) observed 16.0% undercall and 41.0% overcall by cervical biopsy compared to LEEP and / or LETZ. Although several studies have reported undercall of 23 to 55.0% in terms of severity of dysplasia for cervical biopsy confirmed CIN 1 to have CIN II to CIN III in LLETZ

specimen (Buxton et al, 1991; Chappatte et al. 1991; Massad et al, 1996; Barker et al. 2001; Wright et al. 2002) The studies using the two-tier system have reported presence of HSIL in 21 to 42.0% of the excised specimen, when LSIL was reported on colposcopic directed biopsy (Higgins et al, 1994; Baldauf et al, 1997; Ihonor et al, 1999).

The percentage of undercall for cervical punch biopsy compared to final cervical excision procedure found in this study is also very high and it could be due to failure to biopsy the most abnormal area at the time of cervical punch bipsy. The majority of women in this study had one cervical punch biopsy performed and only 11 (1.2 %) women had three biopsies performed at the same visit **(Figure 5, page 65**). To increase the sensitivity of cervical punch biopsy more than one biopsy is indicated (Gage et al, 2006; Jeronimo & Schiffman, 2006). Such a high rate of undercall at punch biopsy is worrisome as it would lead to inadequate treatment resulting in persistence of high grade lesions and may lead to progression to invasive disease.

Explanation of possible reasons for undercall and overcall in these procedures

The following possible reasons for undercall and overcall have been discussed in the published literature. The overcall could have resulted due to "removal of the focus with the most severe lesion, complete removal of the lesion by biopsy or resolution of lesion because of inflammation, secondary to cervical punch biopsy" (Ihonor et al, 1999). Undercall may be due to failure to biopsy the most abnormal area, inability to detect a tiny subtle HSIL occurring in the midst of large LSIL, location of a lesion high up in the endocervical canal or failure to biopsy all cervical lesions before excision procedure. Such undercall or overcall may not necessarily reflect the colposcopist's skill. Colposcopy has better sensitivity for HSIL compared to LSIL and that could be due to easily identifiable features of HSIL (Higgins et al, 1994; Hopman et al, 1995; Cetzin et al, 1998; Mitchell et al, 1998; Boonlikit et al. 2006; Gage et al, 2006; Jeronimo & Schiffman, 2006**).**

In this study, the discordance found between the procedure results is likely as a result of those suggested by clinical explanations (Ihonor et al, 1999, Higgins et al, 1994; Hopman et al, 1995; Cetzin et al, 1998; Mitchell et al, 1998; Boonlikit et al. 2006; Gage et al, 2006; Jeronimo & Schiffman, 2006). If the result of the final cervical excision procedure was influenced by the final colposcopist and pathologist being aware of the results of the earlier procedures, this would have tended to increase the degree of

agreement between the procedures, and leading to a reduction in the degree of undercall and overcall observed, but this was not the case in this study.

Clinical use of the various diagnostic procedures

A stepped approach is taken to diagnose and treat cervical dysplasia (**Figure 2, page 18**). Initially Pap smear is used to screen women followed by colposcopic examination of those women whose Pap smear is reported as abnormal. If colposcopic impression is not negative then suspected cervical lesions are biopsied under colposcopic guidance and sent for histopathological examination. If there is no visible lesion on colposcopy and Pap smear was abnormal, women may undergo ECC. Based on histopathology of colposcopic guided cervical punch biopsy or of ECC women will be advised to undergo final cervical excision procedure (LEEP, LEEP biopsy, or cold knife cone). At each step women may receive a negative diagnosis and follow up colposcopy advised or receive a positive diagnosis and be advised to have treatment (final cervical excision procedure) or else receive an unclear diagnosis and go on to have excision procedure as a diagnostic test. Thus at each step women with negative diagnoses can be removed from further diagnostic processes and sent for routine screening. The goal is to perform invasive procedure (LEEP, LEEP biopsy, cold knife cone) only in women with severe cervical dysplasia (HSIL), unclear diagnosis, or if concern is about possibility of missing invasive cancer and because of concern about inherent adverse outcome with the final cervical excision procedure (**page 17)**.

Characteristics of study population in comparison to other published studies

As described in the method section (**page 55**) only women who underwent all three diagnostic or therapeutic tests are included in this study as per study objective. Performing cervical excision procedure in patients without cervical dysplasia cannot be justified because it is an invasive procedure and has associated side effects and complications. Subjecting disease negative patients to an invasive procedure is not only unethical but also a monetary burden to our health care system. This means that all women included in this study has had cervical dysplasia diagnosis and therefore the study is subjected to verification bias **(Refer to page 118**). In almost all published studies which have examined degree of agreement and / or percent agreement between these three diagnostic and or therapeutic procedures, the authors have used a similar study design (all study subjects had at least one diagnostic test positive); therefore these published studies are similarly subjected to verification bias. This study is also subjected to low kappa value despite higher percent agreement between the three procedures because of highly selected study subjects (all women who has had all three procedures, high prevalence of cervical dysplasia in study subjects) in comparison to a screening population where cervical dysplasia is a rare disease.

In this study the mean interval between initial colposcopic assessment and the final cervical excision procedure (assessment treatment interval) visit was 67.9 days, which is

similar to several other reported studies (Baldauf et al, 1997; Cetzin et al, 1998; Ihonor et al, 1999; Massad, Collins, & Meyer, 2001). This similarity may be due to the period of time required between colposcopy and availability of histopathology results of cervical punch biopsy before decision for final procedure could be made and variable waiting time before the procedure.

The demographic characteristics of this study cohort were similar to those reported in several earlier studies. The mean age of this study population was 32.2 years (range 16 to 80 yrs.), which is similar to reported by (Denny et al, 1995; Ihonor et al, 1999; Barker et al, 2001; Massad, Collins, & Meyer, 2001; Costa et al, 2002; Zaitoun et al, 2006; Tyler et al, 2007). A few authors have examined slightly younger cohort with mean age of 23.8 to 26.5 years (Chappatte et al, 1990; Higgins et al, 1994). Boonlikit et al. (2006) studied a slightly older cohort with mean age of 41.0 years (16 to 81). In this study 580 (63.3%) women were non smokers and 327 (35.7%) were current or former smokers, which were similar to those reported by (Massad & Collins, 2003). Cigarette smoking has been identified as a cofactor that promotes progression of cervical carcinogenesis (Ho et al, 1998; Olsen et al, 1998; Trimble et al, 2005).

The percentage of referral cytology with HSIL was much higher in this study cohort. Compared to LSIL and ASCUS, HSIL accounted for 494 (54.4%) of referral Pap smear, and LSIL for 263 (28.7%). Denny et al. (1995) observed 14.0% of referral Pap as persistent CIN 1, 26.0% as CIN II, and 60.0% as CIN IIII, which is similar to our study results. The other authors in contrast have reported smaller percentage (19 to 25.0%) of

HSIL referral Pap (Higgins et al, 1994; Ferenczy et al, 1996; Massad & Collins 2003). This difference could be due to our centre (CHR and TBCC) algorithms of not seeing and treating LSIL until it is persistent **(appendix F),** whereas other centres may have different colposcopy referral guidelines resulting in more colposcopy for women with LSIL and ASCUS.

Results of studied procedures in comparison to other published studies

In this study colposcopic impression was similar to that reported by (Massad & Collins, 2003). Cervical punch biopsy and or ECC histopathology diagnosis was similar to reported by (Cetzin et al, 1998; Boonlikit et al, 2006). Massad & Collins (2003) reported 15.0% rate of HSIL and benign in 17.0%, which is quite different from this study cohort (64.8% HSIL and negative in 3.9%), and other reported studies. This discrepancy could be due to a higher percentage of severe dysplasia in the referral cytology, indicating this study population was different in severity of cervical dysplasia. This study population was also different in terms of indications for final cervical excision procedure (more HSIL than LSIL), that could be due to CHR guidelines for treatment of cervical dysplasia, which is to treat LSIL only if it is persistent and also to use laser ablation in selected cases instead of cervical excision as a definitive modality to minimize long term side effects of final cervical excision procedure.

The final cervical excision procedure histopathology was reported as HSIL in 653 (71.1%) women, which was similar to other reported studies (Fereneczy et al, 1996; Cetzin et al, 1998; Barker et al, 2001). Several published studies have reported very high percentages of negative histopathology (13.6 to 40.7%), which is quite concerning (Alvarez et al, 1994; Fereneczy et al, 1996; Cetzin et al, 1998; Barker et al, 2001; Boonlikit et al, 2006). This study results show much lower (2.6%) than other reported rates of negative histopathology although similar to (Barker et al, 2001). This indicates a lower risk of overtreatment with less likelihood of adverse consequences. Possible

explanations for negative histopathology of final cervical excision procedure include regression of HSIL, complete removal of small focus of HSIL by cervical biopsy alone or secondary to the inflammatory process resulting from the biopsy.

In this study cohort underlying unsuspected invasive carcinoma on final cervical excision procedure was diagnosed in only four (0.4%) women on final cervical excision procedure, which was significantly lower than reported incidence of 1 to 3.0% (Gunasekera et al, 1990; Luesley et al, 1990; Buxton et al, 1991; Chappatte et al, 1991; Denny et al, 1995; Kennedy et al, 1995; Ferenczy et al, 1996; Maluf et al, 2004). Only one (0.1%) women was found to have microinvasive carcinoma and 11(1.3%) women were noted to have AIS on final cervical excision procedure histopathology, which is similar to other study reports (Ferenczy et al, 1996; Maluf et al, 2004). Maluf et al. (2004) reported microinvasive carcinoma in 5.1% of the LEEP specimens.

In this study cervical punch biopsy accurately identified all 11 (1.2%) cases of AIS but missed three (0.3%) invasive and one (0.1%) microinvasive carcinoma, which was diagnosed on final cervical excision procedure. Costa et al. (2003) observed 43 missed squamous cell carcinomas among 739 CIN 2-3 biopsies (prevalence of 5.8%). Chappatte et al. (1991) reported that cervical biopsy missed three cases (3%) of microinvasive carcinoma, which were diagnosed on LLETZ. Boonlikit et al. (2006) reported eight cases of missed microinvasive and 17 (6.9%) cases of missed invasive carcinoma on cervical biopsy, which is significantly higher than this study result and several other published studies (Prendeville et al, 1989; Gunasekera et al, 1990; Chappatte et al, 1991; Buxton et

al, 1997; Barker et al, 2001; Wright et al, 2002; Costa et al, 2003; Soto-Wright et al, 2005). The lower rate of invasive and microinvasive carcinoma in this study could be due to better trained colposcopists triaging patients appropriately. All women in this study had either cervical biopsy (88.4%) and / or ECC (11.6%) excluding invasive carcinoma prior to cervical excision procedure. In those women who had negative colposcopic impression (11.5%), a cervical punch biopsy was not done but ECC was still performed. There is evidence that performing more than one cervical punch biopsy is better to improve diagnosis of cervical dysplasia. In this study 218 (23.8%) women had two biopsies and only 11 (1.2 %) had three biopsies performed **(Figure 6, page 78)**. It could also reflect pathologists' skill in not missing invasive carcinoma in cervical biopsy specimens.

Status of margins of final cervical excision procedure specimen post procedure ECC in comparison to other published studies

The rate of involvement of endocervical margin (27.2%) and ectocervical margin (20.9%) of final cervical excision procedure specimen **(Table 11, page 80)** was similar to the reported rate of 23 to 50.0% in the literature (Felix J, 1994; Baldauf et al, 1997; Dietrich et al, 2002; Boonlikit et al, 2006). Deep endocervical gland involvement in final histopathology specimen was observed in 69 (7.5%) women **(Table 12, page 81)**, which is similar to the results reported by other authors (Demopoulos, Horowitz, & Vamvakas, 1991; Mahadevan et al, 1993; Massad et al, 1996; Zaitoun et al, 2000; Anderson et al, 2004).

Indications of final cervical excision procedure

The indications for final cervical excision procedure were HSIL in 594 (64.8%), LSIL in 109 (11.9%), and others (included condyloma, benign atypia, and HPV changes, SIL unqualified, SIL unqualified favouring HSIL, or LSIL, immature squamous metaplasia with or without atypia, mature squamous epithelium, microglandular hyperplasia, tubal metaplasia), in 178 (19.4%) women. This is similar to as reported by (Barker et al 2001; Dietrich et al, 2002; Costa et al, 2003). This result is not in complete agreement with recommendations of "2003 guidelines for colposcopy management of CHR & TBCC" in terms of indications for cervical excision procedure. These guidelines recommend performing cervical excision in cases of HSIL and AIS and not LSIL **(Appendix F**). Similarly the SCC guideline recommends cervical excision procedure in cases of HSIL, ASC-H, persistent LSIL, and AIS (**Appendix G**).

This small discrepancy in indication for cervical excision procedure could represent individual colposcopist unawareness of the existing guideline or simply wish to practice colposcopy based on own clinical experience and comfort level.

Methodological Choices that may have Influenced Study Findings

Methodological differences may be responsible for some of the differences in this study results and some of the reported studies. Such differences include: type of research design, lack of use of RCI in colposcopy interpretation, procedure performed by novice versus expert, absence of pathology review, and length of follow up.

Research Design

The retrospective nature of this study in comparison to some other prospective studies (Chappatte et al, 1991; Stoler et al, 1991; Ferris et al, 1996; Heatley & Burke 1998; Ihonor et al, 1999; Massad & Collins, 2003; Baum et a., 2006; Boonlikit et al, 2006; Mousavi et al, 2007) might have affected the result. The information was collected from the patient's chart: the accuracy of the information could have influenced some of the study findings. Some of the information was also missing or incomplete such as, any side effect or complication after cervical excision procedure, size of the excised specimen. This resulted in failure to assess rate of complication associated with cervical excision procedure at our centre and compare it to the reported complications in literature to assess the quality of colposcopic practice at CHR. The study population (being all women positive for disease by one diagnostic test) also introduced verification bias, but it did not alter assessment of study objective (degree of agreement between procedures) by kappa statistics (kappa is not affected by verification bias).

Lack of use of RCI for colposcopy interpretation

Other authors have suggested that more accurate colposcopic diagnosis can be achieved through the use of RCI (a specific scoring system for colposcopic examination), which was not used by the colposcopists in the CHR. Mousavi et al. (2007) prospectively assessed the strength of agreement between colposcopy and cervical biopsy by comparing RCI and general colposcopy, **(Table 5, page 40)** and observed better kappa in the RCI group. If RCI had been used in this study to improve the accuracy of colposcopic diagnosis (Mousavi et al. 2007), it is possible that the degree of agreement between colposcopic impression and the other two procedures would have been improved and discordance reduced. In this study there was a high overcall rate for colposcopic impression, and this would be expected to be reduced by improving the accuracy of colposcopic reporting.

Procedures performance by novice versus expert

In many women cervical biopsies were performed by residents or gynaecologic oncology fellows under the direction of faculty and biopsy might have missed the most abnormal appearing area (highest grade assigned by the supervising attending). However, a study done by Baum et al. (2006) reported small differences in the accuracy of

colposcopic assessment based upon the level of resident training. Jeronimo & Schiffman, (2006), advocated more than one biopsy for both novice and experienced colposcopists to improve the sensitivity of colposcopy as the colposcopic appearance is often complex and the most abnormal area may be small. Massad and Collins (2003) reported 23.0% of women found to have more severe lesion than faculty colposcopists suspected, suggesting that inaccurate biopsy cannot necessarily explain our findings.

Absence of pathology review

Review of the biopsy or cervical excision procedure histopathology by a single pathologist was not undertaken. It is also not known how many pathologists were reporting the histopathology and how many were specialized in gynepathology. The absence of central pathology review might have limited the validity of our data. Although all pathologists were board certified in anatomic pathology and were supposed to use common systems for grading cervical biopsies and final cervical excision specimen, some of the histopathology reports were not consistent, and margin status and cervical glandular involvement was missing. It has been shown that expertise in histological diagnosis varies and diagnosis may be poorly reproducible even among gynaecologic pathologists. There is poor to moderate inter and intraobserver agreement for histopathology interpretation, even between trained pathologists (Ismail et al, 1989; McCluggate et al, 1996; Stoler et al, 2001; Anderson et al, 2004) as histopathological interpretation is also subjective.

Strengths and Limitations of the Study

This section discusses the study results relative to validity including both confounding and bias, study strengths and weaknesses.

Validity

Internal validity addresses whether or not the results of a study are true for the individuals under study, and not likely due to confounding or bias (Gay, J. 1999).

Confounding

Confounding occurs when there is a distortion in the results of a study because of the presence of another risk factor for disease which is associated with both the risk factor under study and the outcome, but is not a part of the causal pathway (Gay, J. 1999). A possible confounder in this study was colposcopists' and pathologists' skill level. An important aspect of the study was to include all 15 of the colposcopists who performed colposcopy at the WHC and all three who performed colposcopy at TBCC colposcopy clinic. The histopathology specimens of cervical punch biopsy and final cervical excision procedure were reported by many different pathologists **(**not reviewed by a single pathologist or a group of gynaecologic pathologists) that could have confounded the study result.

Bias

Bias is a systematic error whereby the results that are obtained for a study differ systematically from the truth (Gay, J. 1999). A number of types of bias threaten the validity of the study: verification bias, selecting bias, sampling bias, and recall bias etc.

Verification bias

Verification bias is associated particularly with screening tests because screening test is performed on a healthy symptomless population and it leads to further diagnostic work up for those who has a positive screening test. In this context gold standard procedure is only performed on those with positive diagnostic test result. It results in gold standard test being performed to confirm disease status on a very small number of participants (a subset of subjects) with normal diagnostic test results, which means that the number of "false negatives" is very low (Cronin & Vickers 2008). If the study design includes only women with one or more positive screening tests referred for further diagnostic tests, it prevents the unbiased estimation of absolute sensitivity (falsely elevated) and specificity (falsely decreased). This bias is introduced by the fact that only a fraction of women will be tested negative by both tests and majority of those will be at least one test positive (100% for this study as specified in the study protocol and that was the study objective).

Ideally a possible solution to correct for verification bias is to include a random sample of diagnostic test-negative subjects (unverified subjects) to undergo disease

verification by gold standard. There will be a need to have sufficiently large sample size to provide enough an adequate number of false negatives to estimate sensitivity because in case of small number of false negatives standard methods of correction of verification bias are not adequate. By including a large number of disease negatives to improve sensitivity w ill mean subjecting this population to an unnecessary invasive procedure (gold standard) and possible side effects and complications. It will also result in extra cost to health care system (Cronin & Vickers 2008).

To correct verification bias the assumption that those women without final cervical excision procedure are likely to have the same prevalence of cervical dysplasia as those women who underwent cervical punch biopsy and / or ECC is not true, because the decision to perform cervical punch biopsy was conditional on the colposcopist's impression during colposcopy. The standard correction process for verification bias is not valid for histological diagnosis (Lizmer et al, 1999; Ratnam et al, 2000; Franco, E.L. 2003). In this study primary objective was to assess the agreement between three procedures by kappa statistic which is not affected by verification bias and neither PPV nor NPV are affected by verification bias. As the verification bias in this study is caused by the fact that all women with test positive (100% positive with cervical punch biopsy and / or ECC as specified in the protocol) were referred for final cervical punch biopsy verification, which decreased the relative proportions of negative subjects.

To explain the effect of verification bias on sensitivity and specificity (Ratnam et al, 2000), created a hypothetical situation in which a single test with 80% sensitivity and

67% specificity were applied to a population of 1000 subjects with 10% cervical dysplasia prevalence. With gold standard verification of the disease status (Ratnam et al, 2000) allocated the frequencies of true positives, true negatives, false positives, and false negatives of 80, 600, 300, and 20, respectively. The authors then randomly restricted verification to 80% of those testing positive and 10% of those testing negative, leading to screening frequencies of 64, 60, 240, and 2, respectively. This increased the sensitivity to 97% and decreased specificity to 20%. The value for PPV (21%) and NPV (97%) are same in both scenarios indicating that PPV and NPV are not affected by the verification bias.

Selection bias:

This is a statistical bias in which there is an error in choosing the individuals or groups to take part in a research or study. The term "selection bias" most often refers to the distortion of a statistical result, as a consequence of the method of collecting samples. This bias affects the internal validity of the study results. In this study all eligible women who has had gold standard test (final cervical excision procedure) performed between January 2003 to December 2004 in WHC and TBCC were included, thereby eliminating selection bias. Only five women with invasive cancer and 11 with adenocarcinoma in situ were excluded before final statistical analysis, which is quite small number and unlikely to introduce selection bias in this study.

Sampling bias:

This is a systematic error and it can be present when some members of the population are less likely to be included than others due to non random sample or when not all patients presented with relevant conditions are included in order of entry. This bias affects the external validity of the study results. Although this study was performed in a selected population as per study protocol and only included those women who underwent the gold standard test, in fact it did include all those women who had pap smear performed and processed in one of the laboratories of CHR and were referred to either WHC or TBCC as a result of abnormal pap smear so it is not subjected to sampling bias. TBCC patients' population comprises of mainly women with higher grade of cervical dysplasia and by including those women this study does eliminate sampling bias.

Recall bias:

This was controlled as all the information was retrieved from the patient's charts and women were not asked for any information from their memory (bleeding, fever, pain, dysmenorrhoea post cervical excision procedure). All the information present in the chart was recorded at the time and not from memory of any clinical staff, that also reduces the possibility of recall bias in this study, although our study design cannot exclude the possibility of some bias in reporting of symptoms to clinic staff.

Study Strengths

Despite the methodological issues discussed above, the results of this research adds to the body of existing literature and answers an important clinical question because it suggests colposcopic impression cannot be considered a reliable substitute for cervical punch biopsy, and confirms the poor agreement among three procedures used to manage cervical dysplasia. The use of a descriptive retrospective chart design with large sample size (n =917) was a major study strength, despite limitations of retrospective chart review. The retrospective design of this study was practical, relatively inexpensive, quick, and ethical. The study sample included all women who presented in the particular time period with a variety of characteristics and from various sectors of the population in the CHR. It was therefore quite representative of the population in the CHR.

A major strength of the study was that there were only a small amount of missing data for most of the study variables and a systematic data cleaning process was carried out. All referral Pap smears of study population were reported from a centralized lab in the CHR which uses standard reporting format and may have reduced the observer bias.

Use of excision procedure histopathology as a gold standard was another major study strength. The design of the study enabled us to determine whether colposcopic impression predicts the histopathological proven diagnosis on cervical punch biopsy and final cervical excision procedure histopathology. Our study only analyzed perfect agreement and not within one degree unlike other reported studies **(Table 4, page 22 to**

25), which makes clinical sense in the two tier system reporting of cervical punch biopsy and final cervical excision biopsy histopathology. This will be of help in making decisions to perform cervical excision procedures in the management of women with cervical dysplasia, since in most circumstances LSIL does not necessarily require an excision procedure, whereas HSIL does require an excision procedure. No Canadian study has assessed agreement for these three diagnostic and / or therapeutic procedures (Benedet, Matisic & Bertrand, 2004).

Study Limitations

The finding of the study in terms of strength of agreement is similar to that reported in published literature. There are some limitations of this study that should be considered. The study design of retrospective chart analysis is associated with general limitation of being dependent on the accuracy and completeness of data that have been collected in the past (existing information in patients' records). This resulted in some important information being unavailable (such as cervical excision procedure related complications i.e. bleeding, infection, fever etc.) and limited our ability to report on complication rate for this study cohort. In particular, long term complications occurring after LEEP were not recorded in the chart. Only in a few cases was bleeding noted and it seems that either woman never reported if they had complications, or went to see their family doctor or walk-in clinic. Also it is possible that women with milder post cervical excision infection, bleeding etc., do not seek medical attention.

The study did not exclude any women whose final cervical excision specimen was not intact or had multiple cautery artefacts not limited to the margin. This may have interfered with the accurate diagnosis and grading of cervical dysplasia as cautery artifacts may partially or totally obscure the disease and may also have been interpreted as negative cervical excision specimen. This would have increased the overcall rate of cervical punch biopsy and /or ECC.

As this was a retrospective chart review, colposcopists were not blinded to the referral cytological diagnosis, but this would be expected to improve colposcopic agreements, which was not the case. Lack of expertise in colposcopy may explain our findings, but in reality colposcopy was performed by 18 experienced colposcopists, 15 of them were specialists in obstetrics and gynaecology and three were gynaecologic oncologists and all of them have been performing colposcopy for many years.

Appropriateness of the statistics and other tools used

Kappa varies with prevalence and kappa will be lower in a high prevalence population and higher in a lower prevalence population. In the disease-free population, agreement will be difficult to determine as a result of little variation in the distribution of results. Kappa is not an appropriate measure of agreement between tests in a disease-free population alone. This study cohort included only women who underwent final cervical excision procedure (highly selected population) and has had one or more prior positive diagnostic tests, so kappa was an appropriate statistical measure of agreement between different modalities with more than two outcomes. “Overall percent agreement” is not an appropriate measure for degree of agreement as it is not a statistical tool and neither it adjusts for disagreement nor takes in account agreement by chance in contrast to kappa. As most of the referenced studies have reported overall percent agreement, in this study overall percent agreement was also estimated to compare across published studies.

"See and Treat" Clinics

"See and treat single visit" practice has been advocated for treating HSIL in high risk and poor compliance patient populations and has shown to reduce the number of colposcopy visits with cost reduction and decrease in anxiety (Luesley et al, 1990). Brewster et al. (2005) performed a randomized controlled trial in the USA in underserved area to assess the feasibility of HSIL management in single visit in 3521 women between 1999 and 2002. The authors reported that rate of follow up improved in women treated for HSIL and no effect for women with less abnormal results. Ferris et al. (1996) performed a study on 48 patients as an approach of "see and treat" and used LLETZ, based on both abnormal Pap smear results and HSIL on colposcopic findings and found 82.0% agreement with cone histopathology where as with LSIL the agreement was only 48.2%. Previous studies of "see and treat single visit" clinics have shown over-treatment of LSIL and consequently side effects of unnecessary conization (Luesley et al, 1990; Ferris et al, 1996; Holschneider et al, 1999; Ihonor et al, 1999). Bigrigg et al. (1990) reported in a series of 1000 patients on "see and treat" for HSIL, that only 2 to 6% of LEEP specimens was negative for dysplasia which is highly acceptable.

In the study described in this thesis if "see and treat in a single visit" approach could have been applied to this study cohort, it would have resulted in overtreatment of 45 (6.5%) women out of 743 with HSIL, with concern about potential unnecessary complications. It would have also led under treatment of 141 women out of 174 (81.3%) by not performing final cervical excision procedure for those women based on

colposcopic impression of LSIL, others, or negative. Failure to treat HSIL would result in progression to invasive cancer in approximately 17 women out of 141 (10 to 12% of undertreated women) of this study cohort, which is unacceptable.

Future Research Direction

The study showed the poor agreement among three diagnostic and /or therapeutic procedures and highlighted the discrepancies between them. The rate of undercall at colposcopy compared to cervical punch biopsy and at cervical punch biopsy compared to final cervical excision procedure is significantly higher than that reported by most other studies. A further prospective study to investigate the effect of multiple cervical punch biopsies prior to definitive management of cervical dysplasia is necessary. This will further clarify whether, irrespective of colposcopists' skill level, lack of more than one cervical punch biopsy in majority of women in the study population could have resulted in such a discrepancy. Additional research is required to define strategies other than multiple biopsies for improving the agreement between colposcopic impression and cervical punch biopsy diagnosis. Such studies should include use of RCI during colposcopy to evaluate impact on diagnoatic accuracy of colposcopy and review of cervical punch biopsy and cervical excision procedure histopathology by a group of gynepathologist' following a standard protocol to evaluate the impact of pathologist variability on outcome.

Conclusion

This study retrospectively examined the agreement between three different diagnostic and / or therapeutic procedures; colposcopic impression, cervical punch biopsy, and final cervical excision procedure histopathology, for the management of cervical dysplasia in 917 women. The overall degree of agreement (measured by kappa statistics) was poor for all comparisons between the procedures, and these results were supported by the McNemar tests which indicated discordance between results of the procedures. The overall percent agreement was comparatively better for all comparisons, a similar finding to some other reported studies. However the overall percent agreement is not a statistic tool and does not take in account agreement on chance alone (as considerable agreement would be expected by chance alone).

Overall, the results of this study are consistent with previous reports in highlighting the discrepancies between the results of colposcopic impression, cervical punch biopsy, and final cervical excision procedure histopathology. Lack of agreement between different diagnostic procedures could be due to inter and intraobserver variability in reporting of cervical dysplasia grade, and / or due to changes in lesion severity as a result of the natural history of the disease. The study confirms the necessity of undertaking all three procedures in the management of cervical dysplasia. This study further supports the use of more than one biopsy in order to decrease the false negative rate of this procedure, and suggests the use of RCI during colposcopic examination to decrease inaccuracy of colposcopic reporting.

The false positive rate (overcall) for colposcopic impression compared to cervical punch biopsy histopathology for HSIL was 29.0 % and the false negative rate (undercall) was 60.8%. The PPV was 70.9% and NPV of 39.1%. As colposcopy significantly underestimated the severity of lesions, it would result in under treatment of women whose management relied only on colposcopic impression, and it cannot be considered a reliable substitute for cervical punch biopsy. Cervical punch biopsy is associated with minor side effects, and failure to perform a cervical biopsy may result in missing a high grade lesion with more severe consequences (HSIL can progress to invasive cancer in 10-20% of cases; **Table 1, page 10**). The findings from this study further indicate that multiple cervical biopsies including random biopsies should continue to be offered prior to definitive treatment of cervical dysplasia.

A "see and treat in a single visit" approach would not be appropriate in this study cohort, as it would have resulted in overtreatment of 20.8% women and subsequent unnecessary complications. It would have also led to under treatment of 66.2% women by not performing a final cervical excision procedure for them based on negative or low grade colposcopic impression of. The study confirms the current practice of reserving the "see and treat" approach for specific geographical areas and disadvantage populations where women would be unable or unwilling to continue attending a colposcopy clnic for follow-up.

This retrospectively review of charts of women who had a cervical excision done for cervical dysplasia was an ethical option compared to a hypothetically more rigorous

approach of collecting data prospectively and offering all women with abnormal colposcopy to undergo cervical excision procedure. Although this study design introduced verification bias and resulted in higher sensitivity and lower specificity than in a complete population sample, the research primarily set out to examine degree of agreement (k) between three diagnostic and / or therapeutic procedures, which is not affected by verification bias. McNemar's Chi-square tests p-value of < 0.05 indcates that these three diagnostic and / or therapeutic procedures are discordant of each other despite whole study cohort was subjected to all three tests.

This study has added to the literature in terms of confirming the poor agreement among the three diagnostic and / or therapeutic procedures used to manage cervical dysplasia, and suggested that colposcopic impression cannot be considered a reliable substitute for cervical punch biopsy. This study confirms that all three procedures are needed in the management of cervical dysplasia.

References:

Abu, J., Davies Q. (2005) Endocervical curettage at the time of colposcopic assessment of the uterine cervix. **Obstet Gynecol Surv,** 60 (5), pp. 315-320.

Alani, R. M., & Münger, K. (1998) Human papilloma viruses and associated malignancies. **J Clin Oncol**, 16 (1), pp. 330-337.

Alberta Cervical Cancer Screening Program (ACCSP), 2005. Available from: <http://www.cancerboard.ab.ca/cancer/cancer_screening.html> [accessed 20 March 20, 2006].

Alvarez, A.D., Helm, C.W., Edwards, R.P., Nauman, R.W. et al. (1994) Prospective randomized trial of LLETZ versus laser ablation in patients with cervical intraepithelial; neoplasia. **Gynecologic Oncology**, (52), pp. 175-179.

Anderson, M., Jordan, J., Morse, A., et al. (1996) Colposcopic appearances of cervical intraepithelial neoplasia. In: **A Text and Atlas of Integrated Colposcopy**: **For Colposcopists, Histopathologists, and Cytopathologists.** 2nd ed. London, UK: Chapman and Hall Medical, pp. 88-94.

Ang, M.S., Kaufman, R.H., Adam, E., et al. (1995) Colposcopically directed biopsy and loop excision of the transformation zone. Comparison of histologic findings. **J Reprod Med** (40), pp. 167-170.

Arbyn, M., Kyrgiou, M., Simoens, C., et al. (2008) Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: meta-analysis. **BMJ,** (337), p. 1284.

Anderson, C. E., Lee, A. J., McLaren, K. M., et al. (2004). Level of agreement and biopsy correlation using two- and three-tier systems to grade cervical dyskaryosis. **Cytopathology**, (15), pp. 256-262.

Baldauf, J.J., Dreyfus, M. & Ritter, J. (1997) An analysis of the factors involved in the diagnostic accuracy of colposcopically directed biopsy. **Acta Obstet Gynecol Scand**, (76) pp. 468-473.

Barker, B., Garcia, F.A., Warner, J., et al. (2002) Baseline inaccuracy rates for the comparison of cervical biopsy to loop electrosurgical excision histopathologic diagnoses. **Am J Obstet Gynecol,** (187), pp. 349-52.

Barker, B., Garcia, F.A., Lozevski, J., et al. (2001) The correlation between colposcopically directed cervical biopsy and loop electrosurgical excision procedure pathology and the effect of time on that agreement. **Gynecol Oncol**, (82), pp. 22-26.

Barnes, M.N., Robertson, M.W., Naumann, R.W., et al. (1998) Histopathological variables prediction of high grade squamous intraepithelial lesions after large loop excision of the transformation zone. **J Lower Genital Tract Dis, (**2), pp. 93-97.

Baum, M.E., Rader, J.S., Gibb, R.K., et al. (2006) Colposcopic accuracy of obstetrics and gynaecology residents. **Gynaecologic Oncol, (**103), pp. 966-970.

Benedet, J.L., Matisic, J.P. & Bertrand, M.A. (2004) An analysis of 84,244 patients from the British Columbia cytology-colposcopy program. **Gynecol Oncol,** (92), pp. 127-34.

Benedet, J.L., Matisic, J.P. & Bertrand, M.A. (2004) The quality of community colposcopic practice. **Obstet Gynecol, (**103), pp.92–100.

Benedet, J.L., Anderson, G.H., & Boyes, D.A. (1985) Colposcopic accuracy in the diagnosis of microinvasive and occult invasive carcinoma of the cervix. **Obstet Gynecol,** 65 (2), pp. 557-562.

Bigrigg, M.A., Codling, B.W., Pearson, I., et al. (1999) Colposcopic diagnosis and treatment of cervical dysplasia at a single clinic visit, Experience of low-voltage diathermy loop in1000 patients. **Lancet, (**336), pp. 229-231.

Boelter, W.C., and Newman, R.L. (1975) The correlation between colposcopic grading, directed punch biopsy, and conization. **Am J Obstet Gynecol**, 122 (8), pp. 945-946.

Boonlikit, S., Asavapiriyanot, S., Junghuttakarnsatit, P., et al. (2006) Correlation between colposcopically directed biopsy and large loop excision of the transformation zone and influence of age on the outcome. **J Med Assoc Thai,** 89 (3), pp. 299-304.

Bornstein, J., Schwartz, J., Perri, A., et al. (2004) Tools for post LEEP surveillance. **Obstet Gynecol Surv,** 59 (9), pp. 663-668.

Bosch, F.X., Manos, M.M., Muñoz, N., et al. (1995) Prevalence of human papilloma virus in cervical cancer: a worldwide perspective. International biological study on cervical cancer (IBSCC) Study Group. **J Natl Cancer Inst,** 87 (11), pp. 796-802.

Buxton, E.J., Luesley, D.M., Shafi, M.I, et al. (1991) Colposcopically directed punch biopsy: a potentially misleading investigation. **Br J Obstet Gynaecol, (**98), pp. 1273-1276.

Brewster, W.R., Hubbell. F.A., Largent, J., et al. (2005) Feasibility of Management of High-Grade Cervical Lesions in a Single Visit. A Randomized Controlled Trial. **JAMA,** 294 (17), pp. 2182-2187.

Brown, D.R., Shew, M.L., Qadari, B., et al. (2005) A longitudinal study of genital human papilloma virus infection in a cohort of closely followed adolescent women. **J Infect Dis,** (191), pp. 181-192

Burger, M.P.M. & Hollema, H. (1993) The reliability of the histologic diagnosis in colposcopically directed biopsies: a plea for LETZ. **Int J Gynecol Cancer**, (3), pp. 385-390.

Burk, R.D., Ho, G.Y., Beardsley, L., et al. (1996) Sexual behaviour and partner characteristics are the predominant risk factors for genital human papilloma virus infection in young women. **J Infect Dis,** (174), pp. 679-689.

Burghardt, E. (1991) Histopathologic basis of colposcopy. In: **Colposcopy Cervical Pathology Textbook and Atlas**, 2nd ed. New York, NY: George Thieme Verlag, p. 61.

Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council of Canada. (1998, with 2000, 2002 and 2005 amendments). **Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans.** Ottawa, Interagency Secretariat on Research Ethics.

Cervical Cancer in Canada. (1998) **Public Health Agency of Canada** [Internet]. Available from: <http://www.phac-aspc.gc.ca/publicat/updates/cervix-98_e.html> [accessed March 21, 2006].

Cervical Cancer (2004) **Cancer in Alberta: A regional picture** [Internet]. Available from:

<http://www.cancerboard.ab.ca/pdf/cancer_prevention/phi_regional_picture_2004.pdf > [accessed 21 March 2006].

Cervical Cancer (2005) Canadian Cancer Society, national cancer Institute of Canada, Statistics Canada, Provincial/Territorial Cancer Registries, Public Health Agency of Canada, **Canadian cancer Statistics** [Internet]. Available from: <http://129.33.170.38/vgn/images/portal/cit_86751114/60/42/393678947ncic_2005stats_en.pdf> [accessed 21 March 2006].

Cervical Cancer (2009) Canadian Cancer Society, National Cancer Institute of Canada, Statistics Canada, Provincial/Territorial Cancer Registries, Public Health Agency of Canada, **Canadian cancer Statistics** [Internet]. Available from: < http://www.cancer.ca > [accessed 23 September 2009].

Cervical Cancer (2008) Canadian Cancer Society, National Cancer Institute of Canada, Statistics Canada, Provincial/Territorial Cancer Registries, Public Health Agency of Canada, **Canadian cancer Statistics** [Internet]. Available from: < http://www.cancer.ca > [accessed 28 October 2008].

Cervical Cancer Statistics (2007) **Cancer in Alberta: A regional picture** [Internet]. Available from: <http://www.cancerboard.ab.ca/NR/rdonlyres/7E77D82C-5431-4032-B8EE-3FDB50EC5135/0/Stats_CervicalCancer.pdf> [accessed 28 October 2008].

Cervical Dysplasia **Allrefer.com Health, Diseases and Conditions** [Internet]. Available from: <http://health.allrefer.com/health/cervical-dysplasia-info.html> [accessed 21 March 2006].

Cetjin, H.E., Chronopoulos, F.T., Meye,r P.M., et al. (1998) Correlating preoperative cytology and colposcopic biopsy with final histology after conization. **J Lower Genital Tract Dis**, (2), pp. 87-92.

Chappatte, O.A., Byrne, D.L., Raw, K.S., et al. (1991) Histological differences between colposcopic-directed biopsy and loop excision of the transformation zone (LETZ): a cause for concern. **Gynecol Oncol**, (43), pp. 46-50.

Chang. D-Y., Cheng, W-F., Torng, P-L., et al. (1996) Prediction of residual neoplasia based on histopathology and margin status of conization specimens **Gynecol Oncol**, (63), pp. 53-56.

Costa, S, Nuzzo, M.D., Rubino, A., et al. (2003) Independent determinants of inaccuracy of colposcopically directed punch biopsy of the cervix. **Gynecol Oncol**, (90), pp. 57-63.

Creswell, J. W. (2003) A framework for design. In: Research design: **Qualitative, Quantitative, and Mixed Methods Approaches**. 2nd ed. Thousand Oaks, Sage Publications Inc, pp. 2-26.

Cronin, A.M & Vickers, E.C. (2008) Statistical methods to correct for verification bias in diagnostic studies are inadequate when there are few false negatives: a simulation study. **BMC Medical Research Methodology**. (8):75

Demopoulos, R.J., Horowitz, L.F. & Vamvakas, E.C. (1991) Endocervical gland involvement by cervical intraepithelial neoplasia grade III: predictive value residual and / or recurrent disease. **Cancer,** (68), pp. 1932-1936.

Denny, L.A., Soeter, R., Dehaecck, K. & Bloch, B. (1995) Does colposcopically directed punch biopsy reduce the incidence of negative LLETZ? **BJOG,** (102), pp. 545-548.

Diagnosis and treatment of cervical carcinomas. (2006) The American College of Obstetricians and Gynaecologists: Practice bulletin, In: **Compendium of selected publications,** Washington, DC, pp. 453-465.

Dictionary of cancer terms. (2008) **National Cancer Institute** [Internet]. Available from: <http://www.cancer.gov/Templates/db_alpha.aspx?CdrID=46468> [accessed Sept 2008].

Dietrich, C.S., Yancey, M.K., Miyazawa, K., et al. (2002) Risk factors for early cytologic abnormalities after loop electrosurgical excision procedure. **Obstet Gynecol**, 99 (2), pp. 188-192.

Dinh, T.A., Garcia, M.N., Waag, I.M., et al. (1998) Conservative management of positive resection margins after loop electrosurgical excision procedure. **J Lower Genital Tract Dis, (**2), pp. 141-143.

Dodd, L.G., Sneige, N., Villarreal, Y., et al. (1992) Quality-assurance study of simultaneously sampled, non-correlating cervical cytology and biopsies. **Diagnostic Cytopathology**, (20), pp. 138-144.

Dunn, T.S., Killoran, K. & Wolf, D. (2004) Complications of outpatient LLETZ procedure. **J Reprod Med, (**49), pp. 76-78.

Ferenczy, A., Choukroun, D. & Arseneau J. (1996) Loop electrosurgical excision procedure for squamous intraepithelial lesions of the cervix: Advantages and potential pitfalls. **Obstet gynecol,** 87(3), pp. 332-336.

Feinstein A. R., & Cicchetti, D. V. (1990). High agreement but low kappa: I. The problems of two paradoxes. **J Clin Epidemiol,** 43(6), pp. 543-549.

Felix, J.C., Muderspach, L.I., Duggan, B.D., et al. (1994) The significance of positive margins in loop electrosurgical cone margins. **Gynecol Obstet Invest,** *(*37), pp. 270-274.

Ferris, D.G. “Reid’s Colposcopic Index” **Journal of Family Practice**. Available from: < http://findarticles.com/p/articles/mi_m0689/is_n1_v39/ai_15654106> [accessed 16 July 2010].

Ferris, D.G., Cox, J.T., Burke, L., et al. (1998) Colposcopy quality control: Establishing colposcopic criterion standards for the national cancer institute ALTS trial using cervigrams. **J Lower Genital Tract Dis,** (2), pp. 195-203.

Ferris, D.G., Hainer, B.L., Pfenninger, J.L., et al. (1996) 'See and treat' electrosurgical loop excision of the cervical transformation zone. **J Fam Pract,** 42 (3), pp. 253-257.

Fine, B.A., Feinstein, G.I. & Sabella, V. (1998) The pre- and postoperative value of endocervical curettage in the detection of cervical intraepithelial neoplasia and invasive cervical cancer. **Gynecol Oncol**, (71) pp. 46-49.

Fleiss, J.L. & Cohen, J. (1973) The equivalence of weighted kappa and the intraclass correlation coefficient as measures of reliability. In: **Educational and Psychological Measurement,** (33), pp. 613-619.

Franco, E.L. (2003) Human papilloma virus testing for primary screening of cervical cancer precursors. **JNCI** Monographs (31), pp. 89-95

Franco, E.L., Duarte-Franco, E., Ferenczy, A. (2001) Cervical cancer: epidemiology, prevention, and role of human papilloma virus infection. **CMAJ,** (164) pp. 1017-1025.

Gage, J.C., Hanson, V.W., Abbey, K., et al. (2006) the ASCUS LSIL Triage Study (ALTS) Group number of cervical biopsies and sensitivity of colposcopy. **Obstet Gynecol,** 108 (2), pp. 264-272.

Gardeil, F., Barry-Walsh, C., Prendiville, W, et al. (1997) Persistent intraepithelial neoplasia after excision for cervical intraepithelial neoplasia grade III. **Obstet Gynecol, (**89), pp. 419-422.

Gardner, M.J. & Altman, D.J. (1989) Confidence Intervals and Statistical Guidelines. London: Statistics with Confidence. In: **Medical Statistics at a Glance** (2nd ed.) Wiley-Blackwell, Oxford London, pp.

Gay, J. (1999) Clinical epidemiology & evidence-based medicine glossary: **Clinical study design and methods terminology** [Internet]. Available from: < http://www.vetmed.wsu.edu/courses-jmgay/GlossClinStudy.htm> [accessed March 27, 2006].

Gordis, L. (1996) Assessing the validity and reliability of diagnostic and screening tests. In: **Epidemiology.** 2nd ed., Philadelphia, Saunders, pp. 77-79.

Gornall, R.J., Boyd, I.E., Manolitsas, T., et al. (2000) Interval cervical cancer following treatment for cervical intraepithelial neoplasia. **Int J Gynecol Cancer,** (10), pp. 198-202.

Guansekera, P.C., Phipps, J.H. & Lewi, B.V. (1990) Large loop excision of the transformation zone (LLETZ) compared to carbon dioxide laser in the treatment of CIN: a superior mode of treatment. **Br J Obstet Gynecol,** (97), pp. 995-998.

Heatley, M.K. & Bury, J.P. (1998) The correlation between the grades of dyskaryosis on cervical smear, grade of cervical intraepithelial neoplasia (CIN) on punch biopsy and the final histologic diagnosis on cone biopsies of the cervix. **Cytopathology**, (9), pp. 93-99.

Higgins, R.V., Hall, J.B., McGee, J.A., et al. (1994) Appraisal of the modalities used to evaluate an initial abnormal Papanicolaou smear. **Obstet Gynecol**, (84), pp. 174-178.

Holowaty, P., Miller, A.B., Rohan, T., et al. (1999) Natural history of dysplasia of the uterine cervix. **J Natl Cancer Inst,** 91 (3), pp. 252-258.

Holschneider, C.H., Ghosh, K. & Montz, F. J. (1999) See-and-Treat in the Management of High-Grade Squamous Intraepithelial Lesions of the Cervix: A Resource Utilization Analysis. **Obstet Gynecol**, 94, pp. 377-385.

Ho, G.Y., Bierman, R., Beardsley, L. et al. (1998) Natural history of cervicovaginal papilloma virus infection in young women. **N Engl J Med**, 338 (, pp. 423-428.

Hopman, E.H., Voorhorst, F.J., Kenemans, P., et al. (1995) Observer agreement on interpreting colposcopic images of CIN. **Gynecol Oncol,** (58), pp. 206-20.

Hopman, E.H., Kenemans, P. & Helmerhorst, T.J. (1998) Positive predictive rate of colposcopic examination of the cervix uteri: an overview of literature. **Obstet Gynecol Surv, (**53), pp. 97-106.

Howe, D.T. & Vincenti, A.C. (1991) Is large loop excision of the transformation zone (LLETZ) more accurate than colposcopically directed punch biopsy in the diagnosis of cervical intraepithelial neoplasia? **Br J Obstet Gynaecol,** (98), pp. 588-591.

Huang L. & Hwang J. (1999) A comparison between loop electrosurgical excision procedure and cold knife conization for treatment of cervical dysplasia: Residual disease in a subsequent hysterectomy specimen. **Gynecol Oncol,** (73), pp.12-15.

Ihonor, A.O. (1999) A comparative study of the assessment of cervical intraepithelial neoplasia in women having large loop excision of the transformation zone. **J Obstet and Gynecol**, 19 (2), pp**.** 169-171.

Ismail, S.M., Colclough, A.B., Dinnen, J.S., et al. (1989) Observer variation in histopathological diagnosis and grading of cervical intraepithelial neoplasia. **Br Med J, (**298), pp. 707-710.

Jakobsson, M., MsocSci, M.G., Sainio, S., et al. (2007) Preterm delivery after surgical treatment for cervical intraepithelial neoplasia. **Obstet Gynecol, 109 (2),** pp.109:309–13.

Jeronimo, J. & Schiffman, M. (2006) Colposcopy at a crossroads. **Am J Obstet Gynecol,** 195 (2), pp. 349-353.

Jones, B.A. & Novis, D.A. (1996) Cervical Biopsy - Cytology Correlation: A College of American Pathologists Q-Probes Study of 22,439 correlations in 348 laboratories. **Arch Pathol Lab Med**, (120), pp. 523-531.

Kato, I., Santamaria, M., De Ruiz, P.A., et al. (1995) Inter-observer variation in cytological and histological diagnoses of cervical neoplasia and its epidemiological implication. **J Clin Epidemiol,** 48 (9), pp. 1167-1174.

Kenemans, P. & Helmehorst Th. J.M. (1998) Positive predictive rate of colposcopic examination of the cervix uteri: An overview of literature. **Obstet gynecol surv,** 53 (2), pp. 97-106.

Kennedy, A.W., Belinson, J.L., Wirth, S., et al. (1995) The role of the loop electrosurgical excision procedure in the diagnosis and management of early invasive cervical cancer. **Int J Gynecol Cancer,** (5), pp. 117-120.

Kietpeerakool, C., Srisomboon, J., Khobjai, A., et al. (2006) Complications of loop electrosurgical excision procedure for cervical neoplasia: a prospective study. **J Med Assoc Thai,** (89), pp. 583-587.

Kirkup W.S., & Hill, A. S. (1980) The accuracy of colposcopically directed biopsy in patients with suspected intraepithelial neoplasia of the cervix. **Br J Obstet Gynecol,** (87), pp.1-4.

Kiviat N. (1996) Natural history of cervical neoplasia: overview and update. **Am J Obstet Gynecol,** 175 (4), pp. 1099-1104.

Kobak, W. H., Roman, L.D., Felix, J.C., et al. (1995) The role of endocervical curettage at cervical conization for high-grade dysplasia. **Obstet Gynecol,** (85), pp. 197-201.

Korkolopoulou, P., Kolokythas, C., Kittas, C., et al. (1992) Correlation of colposcopy and histology in cervical biopsies positive for CIN and/or HPV infection **Eur J Gynaecol Oncol,** 13(6), pp. 502-506.

Krissi, H., Levy, T., Ben-Rafael, Z., et al. (2001) Fistula formation after large loop excision of the transformation zone in patients with cervical intraepithelial neoplasia. **Acta Obstet Gynecol Scand**, (80), pp. 1137-1138.

Lenehan, P. M., Sykes, G.S., Morris, H.B., et al. (1987) Correlation of colposcopy and histology findings in pre-clinical neoplasia of the cervix. **Eur J Gynaecol Oncol,** 8(2), pp. 87-89.

Landis, J.R. & Kotch, G.G. (1977) The measurement of observer agreement for categorical data. **Biometrics,** (33), pp. 159-174.

Lopes, A., Beynon, G., Robertson, G., et al. (1994) Short term morbidity following large loop excision of the cervical transformation zone. **J Obstet Gynaecol,** (14), pp. 197-199.

Luesley, D.M., Cullimore, J., Redman, C.W., et al. (1990) Loop diathermy excision of the cervical transformation zone in patients with abnormal cervical smear. **BMJ,** (300), pp. 1690-1693.

Lyall, H., Duncan, I.D. (1995) Inaccuracy of cytologic diagnosis in high grade squamous intraepithelial lesions (CIN 3). **Acta Cytologica**, 39(1, pp. 50-54.

Management of abnormal cervical cytology and histology. (2006) The American College of Obstetricians and Gynaecologists: Practice bulletin, In: **Compendium of selected publications**, (66), pp. 603-621.

Mahadevan, N. & Horwll, D.H. (1993) The value of cytology and colposcopy in the follow up of cervical intraepithelial neoplasia after treatment by laser excision. **Br J Obstet Gynecol,** (100), pp. 563-566.

Maluf, P.J., Adad, S.J. & Murta, E.F.C. (2004) Outcome after conization for cervical intraepithelial neoplasia grade III: relation with surgical margins, extension to the crypts and mitoses. **Tumori,** (90), pp. 473-477.

Mariamma J.G., Cragg, C., Wright, C.V., et al. (1991) Cyto-histological correlates in a colposcopic clinic: A 1-year prospective study. **Diagnostic Cytopathology,** 7 (5), pp. 477-481.

Massad, L.S., Halperin, C.J., & Bitterman, P. (1996) Correlation between colposcopically directed biopsy and cervical loop excision. **Gynecol Oncol,** (60), pp. 400-403.

Massad, L.S., & Collins, Y.C. (2003) Strength of correlations between colposcopic impression and biopsy histology. **Gynecol Oncol**, (89), pp. 424-428.

Massad, L.S., Collins, Y.C., & Meyer, P.M. (2001) Biopsy correlates of abnormal cervical cytology classified using the Bethesda system **Gynecol Oncol**, (82), pp. 516-522.

McCluggage, W.G., Bharucha, H., Caughley, L.M., et al. (1996) Interobserver variation in the reporting of cervical colposcopic biopsy specimens: comparison of grading systems. **J Clin Pathol, (**49), pp. 833-835.

Melnikow, J., Nuovo, J., Willan, A.R. et al. (1998) Natural history of cervical squamous intraepithelial lesions: a meta-analysis. **Obstet Gynecol**, 92 (4), pp. 727-735.

Mitchell, M.F., Schottenfeld, D., Tortolero-luna, G., Canto, S.B. et al. (1998) Colposcopy for the diagnosis of squamous intraepithelial lesions: A Meta-analysis. **Obstet Gynecol**, 91(4), pp. 626-631.

Mitchell, M.F., Tortoler-Luna, G., Cook, E., et al. (1998) A Randomized clinical trial of cryotherapy, laser vaporization, and loop electrosurgical excision for treatment of squamous intraepithelial lesions of the cervix. **Obstet Gynecol**, 92 (5), pp. 737-744.

Moore, B.C., Higgins, R.V., & Laurent, S.L. (1995) Predictive factors from cold knife conization for residual intraepithelial neoplasia in subsequent hysterectomy. **Am J Obstet Gynecol,** (173), pp. 361-368.

Moscicki, A.B., Shiboski, S., Hills, N.K., et al. (2004) Regression of low-grade squamous intra-epithelial lesions in young women. **Lancet**, 12; (364), pp. 1678-1683.

Munoz, N., Bosch, F.X., de Sanjose, S., et al. (2003) Epidemiologic classification of human papilloma virus types associated with cervical cancer. **N Engl J Med**, (348) pp. 518-527.

Mousavi, A.S., Fakour, F., Gilani, M.M., et al. (2007) A Prospective Study to Evaluate the Correlation Between Reid Colposcopic Index Impression and Biopsy Histology. **J Lower Genital Tract Dis,** 11(3), pp. 147-150

Murdoch, J.B., Morgan, P.R., Lopes, A., et al. (1992) Histological incomplete excision of CIN after large loop excision of the transformation zone (LLETZ) merits careful follow up, not retreatment. **Br J Obstet Gynaecol,** (99), pp. 990–993.

Myers, E.R., McCroy, D.C., Nanda, K., et al. (2000) Mathematical model for the natural history for the natural history of human papilloma virus infection and cervical carcinogenesis. **Am J Epidemiol,** (151), pp. 1158-1171.

Nash. J.D., Burke, T.W. & Hoskins, W.J. (1987) Biologic course of cervical human papilla virus infection. **Obstet Gynecol**, 69 (2), pp. 160-162.

Nasiell, K., Roger, V. & Nasiell, M. (1986) Behaviour of mild cervical dysplasia during long-term follow-up. **Obstet Gynecol,** 67 (5), pp. 665-669.

Naumann, R.W. & Crispens, M.A. (1996) Treatment of cervical dysplasia with large loop excision of the transformation zone: is endocervical curettage necessary? **Southern Medical Journal**, (86), pp. 961-965

Ngan, H.Y.S., Hsu, C., Cheung A.N.Y., et al. (1993) Correlation between colposcopic and histological diagnosis of loop diathermy excised cervical lesions. **J Obstet Gynaecol**, (13), pp. 462-465

Nelson, G.S., Duggan, M.A. & Nation, J.G. (2006) Controversy in colposcopic management: A Canadian survey. **JOGC**, pp. 36-40.

Ohel, G. (1981) Complications of cone biopsy of the cervix. **SA Med Journal,** pp. 382-383.

Olsen, A., Dillner, J., Skrondal, A., et al. (1998) Combined effect of smoking and human papillomavirus type 16 infection in cervical carcinogenesis. **Epidemiology**, (9), pp. 346–349.

Ostor, A.G. Natural history of cervical intraepithelial neoplasia: a critical review. (1993) **Int J Gynecol Pathol, (**12), pp. 186-192.

Prendiville, W., Cullimore, J. & Norman, S. (1989) Large loop excision of the transformation zone (LLETZ). A new method of management for women with cervical intra-epithelial neoplasia. **Br J Obstet Gynaecol,** 96 (9), pp. 1054–1060.

Reich, O., Lahousen, M., Pickel, H., et al. (2002) Long term outcome after cold-knife conization with involved margins. **Obstet Gynecol**, (99), pp. 193-196.

Reich, O., Pickel, H., Lahousen, M., et al. (2001) Cervical intraepithelial neoplasia III: Long-term outcome after cold-knife conization with clear margins **Obstet Gynecol**, (97), pp. 428 –430.

Reid, R and Scalzi P. (1985) Genital warts and cervical cancer. An improved colposcopic index for differentiating benign papillomaviral infections from high-grade cervical intraepithelial neoplasia. **Am J Obstet Gynecol**, 153(6), pp. 611-618.

Role of loop electrosurgical excision procedure in the evaluation of abnormal Pap test results. (1997) The American College of Obstetricians and Gynaecologists: Committee Opinion Bulletin No. 195, In: **Compendium of selected publications,** Washington, DC,

Sellor, S.J., Mahony, J., Kaczorowski, J. et al. (2000) for the Survey of HPV in Ontario Women (SHOW) Group. Prevalence and predictors of human papilloma virus infection in women in Ontario, Canada. **CMAJ** (163) pp. 503-508.

Sheshadri, V. & O'Connor, D. (1999) The agreement of colposcopic grading as compared to direct biopsy results. **J Lower Genital Tract Dis,** 3 (3), pp. 150-154.

Sideri, M., Schettino, F., Spinaci, L., et al. (1995) Operator variability in disease detection and grading by colposcopy in patients with mild dysplastic smears. **Cancer,** (7, pp. 1601-1605.

Sideri, M., Spolti, N, Spinaci, L., et al. (2004) Interobserver variability of colposcopic interpretations and consistency with final histology results. **J Lower Tract Dis**, 38 (3), pp. 212-216.

Skehan, M., Soutter, W.P., LTM, K., et al. (1990) Reliability of colposcopy and directed punch biopsy. **Br J Obstet Gynaecol,** (97), pp. 811-816.

Solomon, D., Davey, D., Kurman, R., et al. (2002) The 2001 Bethesda System: Terminology for Reporting. **JAMA,** 287 (16), pp. 2114-2119.

Soto-Wright, V., Samuleson, R. & McLennan, R. (2005) Current management of low-grade squamous intraepithelial lesion, high-grade squamous epithelial lesion, and atypical glandular cells. **Clin Obstet Gynecol**, 48 (1), pp.147–159.

Spitzer, M., Chernys, A.E., Shifrin, A., et al. (1998) Indications for cone biopsy: pathologic correlation. **Am J Obstet Gynecol**, 178 (1), pp. 74-79.

Stoler, M.H. & Schillman, M. (2001) Interobserver reproducibility of cervical cytologic and histologic interpretations. **JAMA,** 285 (11,) pp. 1500-1505.

Soutter, W.P., Lopes, A. de. B., Fletcher, A., et al. (1997) Invasive cervical cancer after conservative therapy for cervical intraepithelial neoplasia. **Lancet,** (349), pp. 978-980.

Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests; Guidance for Industry and FDA Reviewers, available from: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071148.htm> [accessed Dec 14th 2009].

Szurkus, D.C., and Harrison, T.A. (2003) Loop excision for high-grade squamous intraepithelial lesion on cytology: Correlation with colposcopic and histologic findings. **AJOG,** 188 (5), pp. 1180-1182

Takami, C.Y., Nieberg, R.K. & Berek, J.S. (1991) Correlation of endocervical curettage with subsequent cone biopsy in the investigation of abnormal cervical cytology. **Int J Gynecol Cancer,** (1), pp. 97-103.

Trimble, C.L., Genkinger, J.M., Burke, A.E., et al. (2005) Active and passive cigarette smoking and the risk of cervical neoplasia. **Obstet Gynecol,** (105) pp. 174–181.

Tyler, L.N., Andrews, N., Parrish, R.S., et al. (2007) Significance of margin and extent of dysplasia in loop electro surgery excision procedure biopsies performed for high-grade squamous intraepithelial lesion in predicting persistent disease. **Arch Pathol Lab Med**, (131), pp. 622–624

Veridiano, N.P., Delke, I. & Tancer, M.L. (1981) Accuracy of colposcopically directed biopsy in patients with cervical neoplasia. **Obstet Gynecol,** (58), pp. 185-187.
Vet, H.C.W. de., Knipschild P.G., Schouten H.J.A., et al. (1990) Interobserver variation in histopathological grading of cervical dysplasia. **J Clin Epidemiol,** 43(12), pp. 1395-1398.

Wallin, K.L., Wiklund, F., Angström, T. et al. (1999) Type-specific persistence of human papilloma virus DNA before the development of invasive cervical cancer. **N Engl J Med**, 341 (22), pp. 1633-1638.

Walboomers, J.M., Jacobs, M.V., Manos, M.M. et al. (1999) Human papilloma virus is a necessary cause of invasive cervical cancer worldwide. **J Pathol**, 189 (1), pp. 12-19.

Wright, T.C., Massad, L. S., Dunton, C.J., et al. (2007) 2006 Consensus guidelines for the management of women with cervical intraepithelial neoplasia. **Am J Obstet Gynecol,** 197 (4), pp. 295-304.

Wright, T.C., Cox, J.T., Massad, S., et al. (2002) 2001 Consensus guidelines for the management of women with cervical intraepithelial neoplasia. **Am J Obstet Gynecol,** (189) pp. 295-304.

Yarnoz, M.C., Cortes, J., Lllompart, M, et al. (1988) The colposcopy and cone biopsy in the diagnosis, treatment, and follow-up of 81 cases of cervical intraepithelial neoplasia. **Eur J Gynaecol Oncol,** 9 (4), pp. 345-349.

Zaitoun, A.M., McKee, G., Coppen, M.J., et al. (2000) Completeness of excision and follow up cytology in patients treated with loop excision biopsy. **J Clin Pathol,** (53), pp. 191-196.

Appendix A: Description of Reid Colposcopy Index (RCI) and overall score and histology

Table 18: Reid Colposcopy Index

Colposcopic signs	**Zero point**	**One point**	**Two points**
Colour	Low-intensity acetowhitening (not completely opaque); indistinct acetowhitening; transparent or translucent acetowhitening Acetowhitening beyond the margin of the transformation zone Pure snow-white colour with intense surface shine (rare)	Intermediate shade - grey/white colour and shiny surface (most lesions should be scored in this category)	Dull, opaque, oyster white; grey
Lesion margin and surface configuration	Microcondylomatous or micropapillary contour1 Flat lesions with indistinct margins Feathered or finely scalloped margins Angular, jagged lesions3 Satellite lesions beyond the margin of the transformation zone	Regular-shaped, symmetrical lesions with smooth, straight outlines	Rolled, peeling edges2 Internal demarcations between areas of differing colposcopic appearance—a central area of high-grade change

			and peripheral area of low-grade change
Vessels	Fine/uniform-calibre vessels4- Closely and uniformly placed Poorly formed patterns of fine punctation and/or mosaic Vessels beyond the margin of the transformation zone Fine vessels within microcondylomatous or micropapillary lesions6	Absent vessels	Well defined coarse punctation or mosaic, sharply demarcated5 – and randomly and widely placed
Iodine staining	Positive iodine uptake giving mahogany brown color Negative uptake of insignificant lesion, i.e., yellow staining by a lesion scoring three points or less on the first three criteria Areas beyond the margin of the transformation zone, conspicuous on colposcopy, evident as iodine-negative areas (such areas are frequently due to parakeratosis)7	Partial iodine uptake - variegated, speckled appearance	Negative iodine uptake of significant lesion, i.e., yellow staining by a lesion already scoring four points or more on the first three criteria

1: Microexophytic surface contour indicative of colposcopically overt cancer is not included in this scheme.

2: Epithelial edges tend to detach from underlying stroma and curl back on them selves. Note: Prominent low-grade lesions often are overinterpreted, while subtle avascular patches of HSIL can easily be overlooked.

3: Score zero even if part of the peripheral margin does have a straight course.

4: At times, mosaic patterns containing central vessels are characteristic of low-grade histological abnormalities. These lowgrade– lesion capillary patterns can be quite pronounced. Until the physician can differentiate fine vascular patterns from coarse, overdiagnosis is the rule.

5: Branching atypical vessels indicative of colposcopically overt cancer are not included in this scheme.

6: Generally, the more microcondylomatous the lesion, the lower the score. However, cancer also can present as a condyloma, although this is a rare occurrence.

7: Parakeratosis: a superficial zone of cornified cells with retained nuclei

Table 19: RCI (overall score) Histology

RCI (overall score)	**Histology**
0-2	Likely to be CIN 1
3-4	Overlapping lesion: likely to be CIN 1 or CIN 2
5-8	Likely to be CIN 2-3

Appendix B: Study Definitions

Adenocarcinoma in-situ (AIS): A group of abnormal glandular cells that remain in the tissue in which they first formed. These abnormal cells may become cancer and spread into nearby normal tissue.

Biopsy: It is the process of removal of a sample of living tissue to be examined under microscope by a pathologist for the purpose of diagnosis.

Calgary Health Region (CHR): The health region for the city of Calgary as well as the rural areas around the city (a total area of about 39,000 sq. km) is CHR. Now this comes under Alberta Health Services. A map of the CHR is shown in **Appendix A**.

Cervix: The lower, narrow end of the uterus that forms a canal between the uterus and vagina. It is lined with two main types of cell: squamous and glandular mucus-secreting cells. The junction between the two types of cell is called the transformation zone (TZ) or squamo-columnar junction (SCJ) and is an area of rapid cell turnover where benign and malignant cellular changes are most likely to occur.

Cervical Dysplasia (preinvasive lesions of the cervix): It is a condition in which abnormal cells grow on the thin layer of tissue that covers the cervix. These abnormal

cells are not malignant and not yet invaded the deeper epithelial tissue or spread to other parts of the body of the cervix, but may become cancer.

Cervical Intraepithelial Neoplasia (CIN): Growth of abnormal cells on the surface of the cervix. Numbers from 1 to 3 have been used to describe how abnormal the cells are and what thickness of the cervical epithelium is involved.

Condyloma: A raised growth on the surface of the genitals caused by human papilloma virus (HPV) infection, also called genital wart.

Cytology (Pap test): Pap tests is a procedure in which cells are scraped from the cervix, stained and examined under a microscope for pathological changes in the cervix, is also known as cervical cytology.

Colposcopy; It is the visual examination of the cervix using "colposcope", an optical instrument that illuminates and magnifies the cervix.

Colposcopic Guided Cervical Punch Biopsy Histopathology: Histopathology (the microscopic structure of tissue read by the pathologist) of the biopsy taken from the most atypical site of the cervix identified by the colposcopists.

Colposcopic Overcall: It is defined as colposcopic impression is more severe than cervical excision procedure histology.

Colposcopic Undercall: It is defined as colposcopic impression is less severe than cervical excision procedure histology

Cone Biopsy (conization): It is the surgical removal (excision) of the cone-shaped uterine cervix, which encompasses both the ectocervix and endocervix; while preserving the uterus.

Cold Knife Cone Biopsy: Cone biopsy performed by knife instead of wire loop

Endocervical Canal: The cavity running the length of the cervix is the endocervical canal and the opening of the endocervical canal into the uterine cavity is known as internal os and opening into the vagina is called the external os.

Endocervical Curettage (ECC): Endocervical curettage is a procedure using a curette (a spoon-shaped instrument) to scrape the mucus membrane of the endocervical canal in order to obtain a tissue sample, which is sent to a pathology lab in formalin.

Endocervical Margin: Internal margin of the cervical cone towards the body of the uterus

Ectocervical Margin: External or outer margin of the cervical cone towards the vagina

Epinephrine: It is a hormone also known as adrenalin and it is used in conjunction with xylocaine as a vasoconstrictor (constricts vessels) to minimize bleeding during cervical punch biopsy and LEEP.

False Positive Rate (FPR): It is the proportion of positive test statistics that are really negative (B / A+B) and can be calculated as (1-specificity)

False Negative Rate (FNR) = It is the proportion of negative test statistics that are really negative (C / C+D) and can be calculated as (1-sensitivity)

Formalin: A 10% solution of formaldehyde in water, which is used to preserve biological specimens

High Grade Squamous Intraepithelial Lesion (HSIL): A precancerous condition in which the cells of the uterine cervix are moderately or severely abnormal.

Histological Overcall: It is defined as cervical punch biopsy is more severe than cervical excision procedure histology.

Histological Undercall: It is defined as cervical punch biopsy is less severe than cervical excision procedure histology

Hysterectomy: A surgical procedure to remove the uterus and the cervix removal of the entire uterus and the cervix is referred as total hysterectomy and removal of the uterus without removing the cervix is known as subtotal hysterectomy

Interobserver variability: Inconsistency between observers (two observers reading a test)

Intraobserver variability: Inconsistency in an observer (single observer reading the test on more than one occasion)

Kappa (k): A measure of agreement between two observers taking into account agreement that could occur by chance (expected agreement).

Kappa = Observed agreement - Expected agreement / 100% - Expected agreement Kappa = Observed agreement - Chance agreement / Total Observed - Chance agreement

Loop Electrical Excision Procedure (LEEP): Cone biopsy performed with a thin wire loop of various diameter through which an electrical current is passed at variable power settings to remove cervical tissue as part of the diagnosis and treatment for cervical dysplasia.

Low Grade Squamous Intraepithelial Lesion (LSIL): A precancerous condition in which the cells of the uterine cervix are slightly abnormal.

Lugol's Iodine: It is an aqueous solution of elemental iodine and potassium iodide and it is taken by glycogen rich epithelium giving brown color to healthy cervical epithelium and is used in colposcopy

Monsel's Solution: An aqueous solution of ferric sub-sulphate ($FeSO_4$), which is used as a haemostatic agent and after cervical biopsy or other cervical excision procedure.

Microinvasive Cancer: Invasive squamous cell carcinoma in which the depth of stromal invasion is minimal.

Positive Predictive Value (PPV): It is the proportion of patients with positive test results who are correctly diagnosed (a / a+b).

Prevalence: The frequency of a condition of interest at a given point in time expressed as a fraction of the number of individuals in a specified group with the condition of interest compared to the total number of individuals in the specified group

Negative predictive Value (NPV): It is the proportion of patients with negative test results who are correctly diagnosed (d / c+d)

Reference standard: The best available method for establishing the presence or absence of the target condition

Sensitivity: It is the proportion of true positives that are correctly identified by the test (a / a+c).

Specificity: It is the proportion of true negatives that are correctly identified by the test (d / b+d).

Three Tier System: A terminological older system for reporting the spectrum of precancerous abnormalities of epithelial cells of the uterine cervix in three categories; CIN 1, CIN II, and CIN III.

True Positive (TP): The number of subjects / specimens with true positive test results

True Positive Result: A positive test result for a subject in whom the condition of interest is present (as determined by the reference standard)

True Negative (TN): The number of subjects / specimens with true negative test results

True Negative Result: A negative test result for a subject in whom the condition of interest is absent (as determined by the reference standard)

Two Tier System: A terminological system for reporting the spectrum of precancerous abnormalities of epithelial cells of the uterine cervix in two categories of LSIL and HSIL.

Xylocaine: It is a common local anesthetic agent and can be injected prior to cervical punch biopsy and LEEP

Appendix C: Map of the Calgary Health Region (Retrieved May 26, 2008. Available at http://www.calgaryhealthregion.ca/corporate/about_us/pdf/map.jpg)

Study ID

Appendix D: Management of Cervical Dysplasia Study Data Collection Form

1. Date of birth YYYY MM DD

2. Date of Colposcopy YYYY MM DD

3. Current smoking status
- Yes ☐
- No ☐
- Missing ☐

4. Current contraception
- Oral contraceptive pill ☐
- Others ☐
- None ☐
- Missing ☐

If others give details

5. Obstetrical history
- Gravidity ☐☐
- Parity ☐☐

6. Menopause
- Yes ☐
- No ☐
- Missing ☐

7. Current HRT
- Yes ☐
- No ☐
- Missing ☐

8. Date of final excision (LEEP) procedure YYYY MM DD

HISTORY PRIOR TO REFERRAL

9. History of abnormal Pap smear
- Yes ☐
- No ☐
- Unknown ☐

Yes No

10. History of prior treatment

Cryotherapy	☐	☐
Laser therapy	☐	☐
Cone biopsy	☐	☐
LEEP	☐	☐
Hysterectomy	☐	☐
Other	☐	☐
Missing	☐	☐

Other, give details: _____

11. History of prior LEEP / LEEP biopsy

Yes	☐
No	☐
Missing	☐
If 'yes', how many?	☐☐ _____

12. Referral Cytology

LSIL	☐
HSIL	☐
ASC-US	☐
ASC-H	☐
AIS	☐
Invasive carcinoma	☐
AGC	☐
Missing	☐

	Yes	No
13. **Endometrial Biopsy**	☐	☐
If yes give details		

INDEX COLPOSCOPY

14. Site of colposcopy

- WHC ☐
- TBCC ☐
- **Colposcopist ID** ☐☐☐☐

15. Colposcopic diagnosis

- NEG ☐
- LSIL ☐
- HSIL ☐
- Microinvasive carcinoma ☐
- Invasive carcinoma ☐
- Missing ☐
- Other ☐

Other, give details: _____

16. Number of cervical biopsies ☐☐

17. Cervical punch biopsy

- No path abnormality ☐
- LSIL ☐
- HSIL ☐
- Adenocarcinoma in situ AIS ☐
- Microinvasive carcinoma ☐
- Invasive carcinoma ☐
- Missing ☐
- Other ☐

Other, give details: _____

18. Pre LEEP ECC

- No path abnormality ☐
- LSIL ☐
- HSIL ☐
- Adenocarcinoma in situ AIS ☐
- SIL unqualified ☐
- Microinvasive carcinoma ☐
- Invasive carcinoma ☐
- Missing ☐
- Other ☐

Other, give details: _____

19. FINAL CERVICAL EXCISION PROCEDURE		
	LEEP CONE	☐
	LEEP BIOPSY	☐
	COLD KNIFE CONE	☐

20. Final cervical excision procedure Pathology

No path abnormality ☐
LSIL ☐
HSIL ☐
Adenocarcinoma in situ AIS ☐
Microinvasive carcinoma ☐
Invasive carcinoma ☐
Missing ☐
Other ☐

Other, give details: _____

21. Resected LEEP or cone margin endocervical

Uninvolved ☐
Involved ☐
Missing ☐
If involved detail:

22. Resected LEEP or cone margin ectocervical

Uninvolved ☐
Involved ☐
Missing ☐
If involved detail:

23. SIL involvement of endocervical gland

Superficial ☐
Intermediate ☐
Deep ☐
None ☐
Missing ☐

24. Post LEEP ECC

No path abnormality	☐
LSIL	☐
HSIL	☐
Adenocarcinoma in situ AIS	☐
Microinvasive carcinoma	☐
Invasive carcinoma	☐
Missing	☐

Other, give details:

RECOMMENDED FOLLOW UP

25. 1ST FOLLOW UP PERIOD	3 MONTHS	☐
	6 MONTHS	☐
	4 MONTHS	☐
	9 MONTHS	☐
	NO SHOW	☐

26. If Show up (Date)

YYYY	**MM**	**DD**

27. Final Colposcopic diagnosis	NEG	☐	
	LSIL	☐	
	HSIL	☐	
	Microinvasive carcinoma	☐	
	Invasive carcinoma	☐	
	Missing	☐	
	Other	☐	
Other, give details:			

28. F/U Recommendation

Repeat colposcopy	☐
Repeat LEEP (excision biopsy)	☐
Discharge screening cytology 12 months	☐
Missing	☐
Other	☐

Other, give details:

If repeat LEEP

29. Date

YYYY	**MM**	**DD**

30. Repeat LEEP findings

- No path abnormality ☐
- LSIL ☐
- HSIL ☐
- Adenocarcinoma in situ AIS ☐
- Microinvasive carcinoma ☐
- Invasive carcinoma ☐
- Missing ☐
- Other ☐

Other, give details: _____

31. Repeat LEEP or cone margin endocervical

- Uninvolved ☐
- Involved ☐
- Missing ☐

If involved detail:

32. Repeat LEEP or cone margin ectocervical

- Uninvolved ☐
- Involved ☐
- Missing ☐

If involved detail:

33. SIL involvement of endocervical gland

- Superficial ☐
- Intermediate ☐
- Deep ☐
- None ☐
- Missing ☐

34. Post Repeat LEEP ECC

- No path abnormality ☐
- LSIL ☐
- HSIL ☐
- Adenocarcinoma in situ AIS ☐
- Microinvasive carcinoma ☐
- Invasive carcinoma ☐
- Missing ☐

RECOMMENDED FOLLOW UP

35. 2ND FOLLOW UP PERIOD	3 MONTHS	☐
	6 MONTHS	☐
	4 MONTHS	☐
	9 MONTHS	☐
	NO SHOW	☐

36. If Show up F/U date

YYYY	MM	DD

37. Final Colposcopic diagnosis	NEG	☐	
	LSIL	☐	
	HSIL	☐	
	Microinvasive carcinoma	☐	
	Invasive carcinoma	☐	
	Missing	☐	
	Other	☐	
Other, give details:			

38. F/U Recommendation

Repeat colposcopy ☐
Repeat LEEP (excision biopsy) ☐
Discharge screening cytology 12 months ☐
Missing ☐
Other ☐

Other, give details:

If repeat LEEP
39. Date

YYYY	MM	DD

40. Repeat LEEP findings

No path abnormality ☐
LSIL ☐
HSIL ☐
Adenocarcinoma in situ AIS ☐
Microinvasive carcinoma ☐
Invasive carcinoma ☐
Missing ☐
Other ☐

Other, give details: _____

41. Repeat LEEP margin endocervical

Uninvolved ☐
Involved ☐
Missing ☐
If involved detail:

42. Repeat LEEP margin ectocervical

Uninvolved ☐
Involved ☐
Missing ☐
If involved detail:

43. Post Repeat LEEP ECC

No path abnormality ☐
LSIL ☐
HSIL ☐
Adenocarcinoma in situ AIS ☐
Microinvasive carcinoma ☐
Invasive carcinoma ☐
Missing ☐

44. 3RD FOLLOW UP PERIOD	3 MONTHS	☐
	6 MONTHS	☐
	4 MONTHS	☐
	9 MONTHS	☐
	NO SHOW	☐

45. If Show up		YYYY	MM	DD
F/U date				

46. Final Colposcopic diagnosis	NEG	☐	
	LSIL	☐	
	HSIL	☐	
	Microinvasive carcinoma	☐	
	Invasive carcinoma	☐	
	Missing	☐	
	Other	☐	
Other, give details:			

47. F/U Recommendation

Repeat colposcopy ☐
Repeat LEEP (excision biopsy) ☐
Discharge screening cytology 12 months ☐
Missing ☐
Other ☐

Other, give details:

48. 4TH FOLLOW UP PERIOD	3 MONTHS	☐
	6 MONTHS	☐
	4 MONTHS	☐
	9 MONTHS	☐
	NO SHOW	☐

49. If Show up		YYYY	MM	DD
F/U Date				

50. Final Colposcopic diagnosis	NEG	☐	
	LSIL	☐	
	HSIL	☐	
	Microinvasive carcinoma	☐	
	Invasive carcinoma	☐	
	Missing	☐	
	Other	☐	
Other, give details:			

51. F/U Recommendation

Repeat colposcopy	☐
Repeat LEEP (excision biopsy)	☐
Discharge screening cytology 12 months	☐
Missing	☐
Other	☐

Other, give details:

52. 5TH FOLLOW UP PERIOD	3 MONTHS	☐
	6 MONTHS	☐
	4 MONTHS	☐
	9 MONTHS	☐
	NO SHOW	☐

If show up		YYYY	MM	DD
53. F/U Date				

55. F/U Recommendation	Repeat colposcopy	☐
	Repeat LEEP (excision biopsy)	☐
	Discharge screening cytology 12 months	☐
	Missing	☐
	Other	☐
Other, give details:		

COMPLICATION AFTER FINAL PROCEDURE (LEEP, LEEP biopsy or cold knife biopsy)

56. Bleeding

Yes	☐
No	☐
Unknown	☐

57. Infection

Yes	☐
No	☐
Unknown	☐

58. Cervical stenosis

Yes	☐
No	☐
Unknown	☐

59. Cervical incompetence

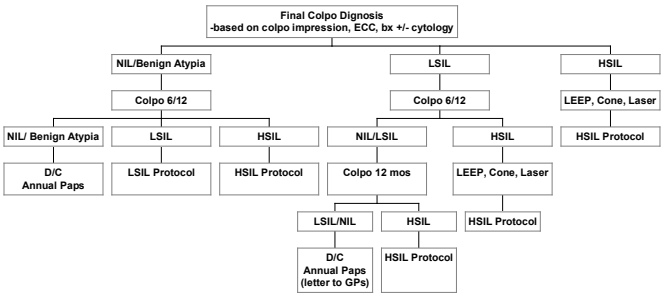
Yes ☐
No ☐
Unknown ☐

60. Other, give details _____

Appendix E: Conjoint Health Research Ethics Board Approval Letter

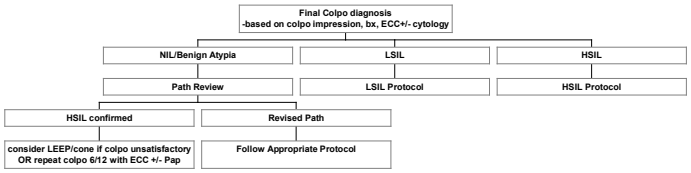
Appendix F: Guidelines for Colposcopy Management CHR & TBCC

LSIL/ASCUS Referral



All patients must have ECC at Colposcopy unless pregnant

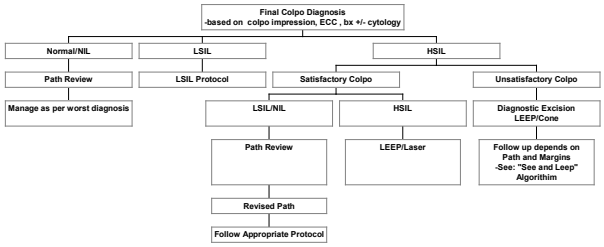
ASC-H



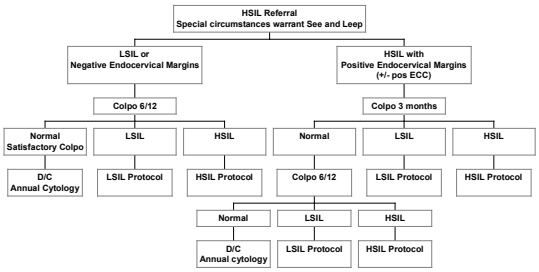
ECC must be performed at colposcopy unless pregnant

HSIL Referral

also see "See and Leep" algorithim



See and Leep



Follow-up After Colposcopic Assessment and Treatment

- After LEEP/Cone
  - Endo/exo cervical margins negative
  - 6 month fu negative
    - Return to annual screening

- After Laser
  - 6 month fu negative
    - Return to annual screening

AGC Referral: Follow-up After Colposcopic Assessment and Treatment

- negative colpo
- negative endometrial biopsy
  - Annual Paps
  - any Pap greater than AGC refer to colposcopy

'Guidelines'

- guidelines are not standard of care
  - management approaches need to be individualized
  - guidelines should never substitute for clinical judgement
- patients should be booked into same colposcopist's clinic if possible
- the colposcopist making recommendations should be the colposcopist performing definitive treatment
- invasive disease needs to be referred to TBCC for Tumor Board Review

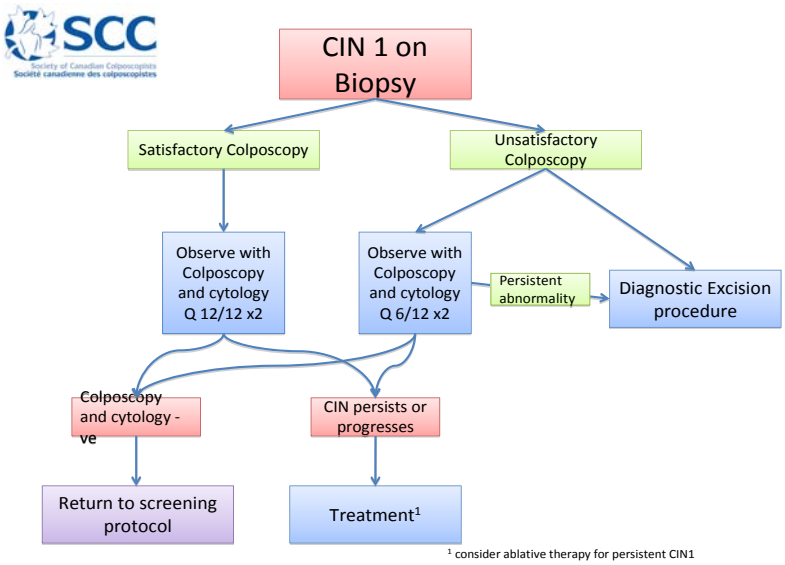
Appendix G: Management of Histological Abnormalities: Society of Canadian Colposcopists (SCC) guideline

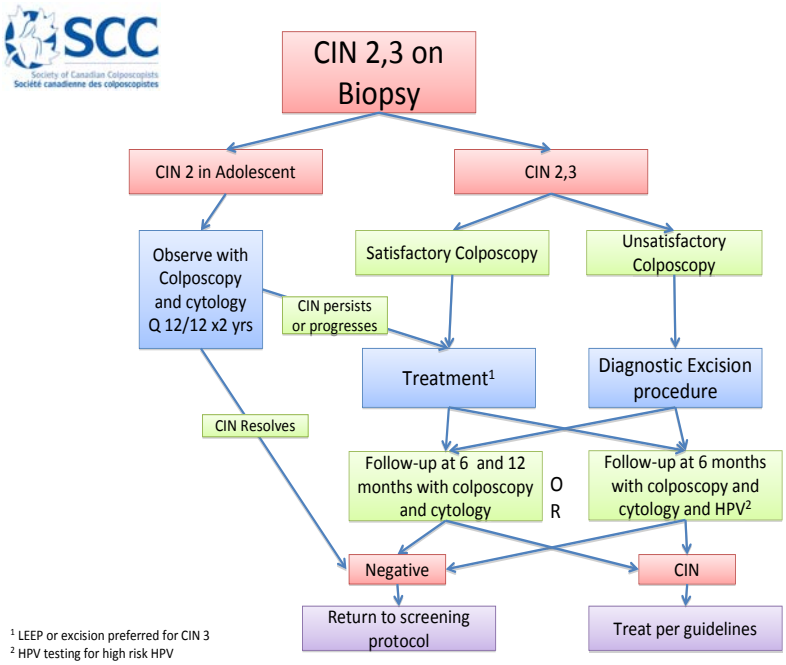
Indications for Colposcopy

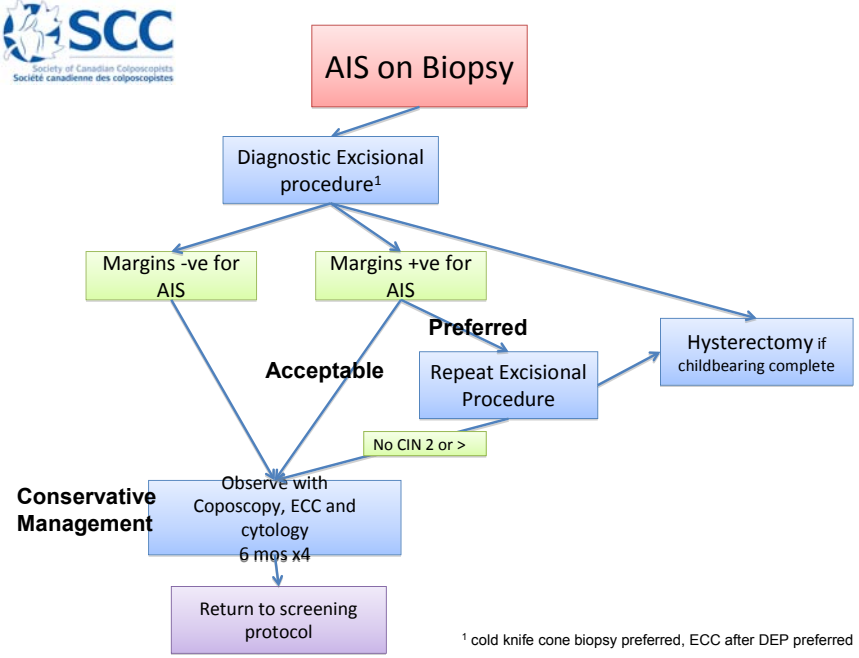
Pap Result	Recommendation
ASC-US	Either: •Repeat in 6 months, if ASC-US or > recommend colposcopy •HPV testing OVER 30 yrs old only, if high risk HPV-DNA $^{+ve}$ recommend colposcopy
ASC-H	colposcopy
LSIL	Repeat in 6 months, if ASC-US or > recommend colposcopy
HSIL	colposcopy
AGC/ AIS	colposcopy
SCC/ Adenocarcinoma	colposcopy

N.B.

1. There are no national accepted guidelines: Adapted from Manitoba, Ontario and Nova Scotia guidelines
2. HPV testing is not universally available except in Newfoundland


CIN 1 on Biopsy
Satisfactory Colposcopy
Unsatisfactory Colposcopy
Observe with Colposcopy and cytology Q 12/12 x2
Observe with Colposcopy and cytology Q 6/12 x2
Persistent abnormality
Diagnostic Excision procedure
Colposcopy and cytology -ve
CIN persists or progresses
Return to screening protocol
Treatment[1]
[1] consider ablative therapy for persistent CIN1


CIN 2,3 on Biopsy
CIN 2 in Adolescent
CIN 2,3
Observe with Colposcopy and cytology Q 12/12 x2 yrs
Satisfactory Colposcopy
Unsatisfactory Colposcopy
CIN persists or progresses
Treatment[1]
Diagnostic Excision procedure
CIN Resolves
Follow-up at 6 and 12 months with colposcopy and cytology
O R
Follow-up at 6 months with colposcopy and cytology and HPV[2]
Negative
CIN
Return to screening protocol
Treat per guidelines
[1] LEEP or excision preferred for CIN 3
[2] HPV testing for high risk HPV


SCC
Society of Canadian Colposcopists
Société canadienne des colposcopistes
AIS on Biopsy
Diagnostic Excisional procedure[1]
Margins -ve for AIS
Margins +ve for AIS
Preferred
Acceptable
Repeat Excisional Procedure
Hysterectomy if childbearing complete
No CIN 2 or >
Conservative Management
Observe with Coposcopy, ECC and cytology
6 mos x4
Return to screening protocol
[1] cold knife cone biopsy preferred, ECC after DEP preferred