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Role of Colposcopy in Diagnosing and Differentiating Types of Cervical Intraepithelial Neoplasia

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Abstract

Background: Preventing cervical cancer hinges on accurately detecting and treating high-grade cervical intraepithelial neoplasia (CIN2+) in individuals referred due to abnormal cervical cytology. While colposcopy has been a cornerstone in this process, concerns have arisen regarding its accuracy in CIN detection and differentiation. This study aims to assess the role of colposcopy in diagnosing and distinguishing various grades of CIN in clinically suspected patients. ***Methods:*** A descriptive cross-sectional study was conducted in the Department of Obstetrics & Gynaecology at Rajshahi Medical College Hospital, Rajshahi, over 12 months from February 2019 to February 2020. The study involved 110 women aged 20-70 years who presented with clinical symptoms indicative of precancerous cervical lesions. Initial evaluations included visual inspection with 5% acetic acid (VIA) and Reid colposcopy. Biopsy samples were collected from the identified lesions using the colposcope, and these samples underwent histopathological examination. The study compared the diagnostic accuracy of colposcopy, including sensitivity, specificity, positive predictive value, and negative predictive value. ***Results:*** Colposcopic evaluations revealed that 80% of the participants exhibited positive lesions (CIN), while 20% displayed negative lesions (normal cervix or cervicitis). Among the colposcopically positive lesions, 50% were graded as CIN-1, 29.5% as CIN-2, and 20.5% as CIN-3. Subsequent histopathological examination of the colposcopy-directed biopsies confirmed CIN or dysplasia in 44.5% of cases. Within this group, 36.7% had CIN-1, 34.7% had CIN-2, 12.2% had CIN-3, 10.2% had invasive squamous cell carcinoma, and 6.2% had carcinoma in situ. Colposcopy demonstrated a sensitivity of 83.7% in diagnosing CIN, with a specificity of 23%, resulting in an overall diagnostic accuracy of 55%. However, when differentiating high-grade CIN from low-grade lesions, colposcopy exhibited a high sensitivity of 92.3% and moderate specificity of 67.7%, with an overall diagnostic accuracy of 75%. ***Conclusion:*** This study concludes that colposcopy is highly sensitive in diagnosing CIN but has limited specificity in excluding patients with normal cervix or cervicitis. Nevertheless, it exhibits optimal sensitivity in differentiating CIN2+ and carcinoma in situ from low-grade lesions and maintains moderate specificity in excluding low-grade CIN. Colposcopy remains a valuable tool in preventing and managing cervical cancer, particularly in identifying high-risk lesions.

Keywords: Colposcopy, Cervical Intraepithelial Neoplasia, Sensitivity, Specificity, Cervical Cancer Prevention.

INTRODUCTION

Cancer is an escalating public health concern, with its prevalence on the rise in both developed and developing nations [1]. Globally, cervical cancer, characterized as a malignant neoplasm of the cervix uteri, ranks as the second most prevalent cancer among women, trailing only behind breast cancer [2]. This alarming trend is particularly pronounced in low and middle-income countries, where resources for prevention, diagnosis, and treatment are often limited or nearly nonexistent. Recent estimates reveal that cervical

cancer accounts for over 500,000 new cases annually, resulting in more than 270,000 deaths, most of which could be prevented [3].

In Bangladesh, cervical cancer is the second most common cancer among women, with approximately 12,000 new cases diagnosed annually [4]. However, it is crucial to recognize that the true burden of cervical cancer in Bangladesh remains significantly underestimated due to the absence of national cancer registries and undiagnosed cases, despite its high prevalence. Limited hospital data from Bangladesh indicate that roughly one-quarter of cancer-related deaths among women can be attributed to cervical cancer, a statistic not accurately reflected in national estimates [5, 6].

The progression from normal cervical epithelial cells to cancer cells occurs gradually over several stages, with cervical cancer commencing in a precancerous phase called dysplasia, which takes several years to develop from normal cells. Diagnosing cancer or precancerous conditions hinges on detecting abnormal cells through Pap smear analysis by cytopathologists. Unfortunately, various reactive, infectious, and inflammatory conditions can produce cells that closely mimic those found in precancerous or malignant lesions, potentially leading to misdiagnosis and endangering patient lives. Such misdiagnoses can have a profound impact on disease management. Timely detection and treatment can significantly reduce cervical cancer mortality, but sampling, screening, and interpretation errors persist [7].

Pap smear cytology's advantage in distinguishing abnormal cells from normal cells is well-established and widely accepted in cervical screening programs. However, the occurrence of false-negative results can unnecessarily delay essential treatment. As such, caution must be exercised when reporting Pap smears. While Pap smear screening remains the primary modality for detecting pre-malignant lesions and cervical carcinoma, its positive predictive value in detecting cervical lesions before they progress to cervical cancer is only 51%, indicating a false-negative rate of 49% [8].

The accuracy of cytological diagnoses on Pap smears largely relies on the morphological characteristics of dysplastic or malignant cells. Cytological changes triggered by infections, drugs, or hormonal fluctuations can closely resemble pre-malignant or malignant changes on a cytomorphological level. In such cases, colposcopy becomes essential for differential diagnosis. However, when abnormal cells are detected, precisely categorizing them as pre-malignant or malignant is highly subjective [2].

Colposcopy, involving the visual inspection of the cervix under magnification, represents one of the initial steps in the diagnostic process for women with abnormal cervical cytology. Colposcopy offers higher sensitivity and specificity than Pap smears and is typically performed when Pap smear results deviate from the norm. Colposcopy is a superior screening method for detecting pre-malignant and malignant cervical lesions. A hospital-based prospective study indicated that colposcopy exhibited an 88% sensitivity and 70% specificity in detecting cervical intraepithelial lesions (CIN), surpassing conventional Pap smears (Bethesda system), which demonstrated a sensitivity of 60% and specificity of 84%. Therefore, colposcopy holds a greater potential for distinguishing precancerous lesions from chronic cervicitis [9].

For a colposcopy to be considered satisfactory, the squamocolumnar junction and the transformation zone must be visible. Well-established criteria for positive colposcopy results include the detection of blood vessel abnormalities (such as punctuation, mosaic, and atypical vessels), whitening of the epithelium following the application of acetic acid, color changes after iodine application, as well as size and demarcation. Several scoring systems for colposcopy have been developed [2]. The primary purpose of colposcopy is to guide subsequent histological sampling, the results of which dictate treatment.

The primary prevention of cervical cancer through HPV vaccination and secondary prevention via screening have proven to be the two most effective strategies for averting invasive cervical cancer. In most developed nations, organized screening initiatives have reduced cervical cancer incidence by enabling early detection and successful treatment of precancerous cervical lesions [1]. In Bangladesh, resources have been developed progressively for the treatment of gynecologic cancers, and population-based cervical cancer screening was launched in 2004. Bangladesh is among the few countries globally implementing Visual Inspection with Acetic Acid (VIA) as the primary screening test in a nationwide community-based screening program. Furthermore, colposcopic evaluation of women with acetowhite areas in squamocolumnar junctions is routinely conducted in most tertiary hospitals before final histopathological evaluation. However, the accuracy of colposcopy has been increasingly questioned. Studies involving loop excision after colposcopy have identified instances where women with CIN2+ and cancer were missed during the colposcopic examination [10]. Biopsies taken from areas that appeared normal during colposcopy have also revealed unsuspected CIN2+. Also, colposcopic lesion grade often fails to accurately predict histology [6]. Experienced colposcopists display only moderate to poor interobserver agreement concerning critical colposcopic assessment components, including lesion grade, characteristics and lesion presence [10]. If colposcopy proves unreliable, preventive strategies may need to be reevaluated. The present study, therefore, endeavors to evaluate the role of colposcopy in diagnosing and

distinguishing different types of cervical intraepithelial neoplasia (CIN).

OBJECTIVES

General objective:

- To determine the role of colposcopy in diagnosing and differentiating cervical intraepithelial neoplasia (CIN) cases.

Specific objectives:

- To observe colposcopic findings of cervical intraepithelial neoplasia (CIN)
- To observe histopathological findings of cervical intraepithelial neoplasia (CIN).
- To find colposcopy's sensitivity, specificity, and positive and negative predictive value in the diagnosis and differentiation of cervical intraepithelial neoplasia (CIN).

MATERIALS AND METHODS

Study Design

This study adopted a cross-sectional observational design to investigate cervical intraepithelial neoplasia (CIN) in N=110 women aged between 20 and 70 years presenting with clinical symptoms suggestive of precancerous cervical lesions. The study was conducted at the Colposcopy Clinic within the Outpatient Department of Rajshahi Medical College Hospital in Rajshahi, spanning 12 months from February 2019 to February 2020. The enrollment criteria were applied to select participants meeting the specified clinical symptom criteria for inclusion in the study.

Inclusion Criteria

- Patients with the following characteristics were included in this study:
- Women aged ranging from 20-70 years
- Post-coital bleeding
- Women with an abnormal cervical cytological report
- VIA positive women
- Intermenstrual bleeding and Unusual vaginal discharge.

Exclusion Criteria

- Patients with the following characteristics were excluded from the study:
- Women with previous treatment of CIN.
- Pregnant women.
- Women with frank growth of cervix with active vaginal bleeding.
- Women who were not physically and mentally fit for giving interview.
- Women who did not wish to be included in the study.

Data Collection

Data were collected via structured questionnaires, interviews, clinical examinations, and laboratory tests. The study's primary objective was to evaluate colposcopy's accuracy in diagnosing and distinguishing cervical intraepithelial neoplasia. Table A outlines the components of test accuracy compared to a confirmed diagnosis, considered the "Gold Standard." It categorizes individuals into true positives (a), false positives (b), false negatives (c), and true negatives (d), shedding light on the screening test's precision in relation to the established diagnosis.

Study Procedure

The study's procedure commenced as patients meeting predefined criteria arrived at Rajshahi Medical College Hospital's Colposcopy Clinic. Ethical clearance was obtained, and participants were purposively selected. Pregnant women and those with active vaginal bleeding or cervical growth were excluded. Complete patient histories were taken, and clinical examinations and relevant laboratory tests were conducted. Visual Inspection with Acetic Acid (VIA) was employed to detect acetowhite areas on the cervix. Patients with positive VIA results underwent colposcopy, during which specific colposcopic findings were assessed. Colposcopically-directed biopsies were taken and sent for histopathological evaluation, classifying tissues according to the CIN classification system. The pathologist was blinded to clinical information and other test results.

Data Analysis

Data were processed and analyzed using the computer software SPSS (Statistical Package for Social Sciences). The test statistics used to analyze data were descriptive statistics (like mean, median, and standard deviation in case of continuous data and frequency with corresponding percentages in case of qualitative data. The accuracy of colposcopy in diagnosing and differentiating was determined by comparing the colposcopy findings with those of histopathology. The components of the accuracy test (sensitivity, specificity, positive and negative predictive values) were computed by respective formulae for the tests as described earlier.

Ethical Considerations

Prior permission was taken from Institutional Review Board (IRB), RMC (Ref. RMC/IRB/2019/19-017/17, Dated: 27-06-2019) Rajshahi to carry out this study. Each patient was informed verbally about the purpose, methods, benefits and risks that might be obtained from the study. They were also informed about their right to withdraw from the project at any time, for any reason. Written consent was obtained from those who voluntarily participated in the study.

RESULT

The present study intended to determine the role of colposcopy in detecting and differentiating different

grades of cervical intraepithelial neoplasia in patients clinically suspected of having the condition. The study included 110 women who were initially evaluated with visual inspection with 5% acetic acid (VIA) followed by evaluation with Reid colposcopy. The biopsy materials from the lesions with colposcope were then subjected to histopathological examination. The two diagnostic modalities were then compared to find colposcopy's diagnostic accuracy (sensitivity, specificity, positive and negative predictive values). The findings of the study obtained from data analysis are documented below:

Table 1: Distribution of respondents by their age (n = 110)

Age (years)	Number	Percentage (%)
≤ 30	18	16.4
31 – 40	62	56.4
41 – 50	20	18.2
> 50	10	9.1

Age distribution shows that about three-quarters (74.6%) of the patients was in their 3rd and 4th decades of life (56.4% were 31 – 40 years old and 18.2% 41 – 50 years). The mean age of the patients were 38.6 ± 8.5 years (range: 20 – 70 years).

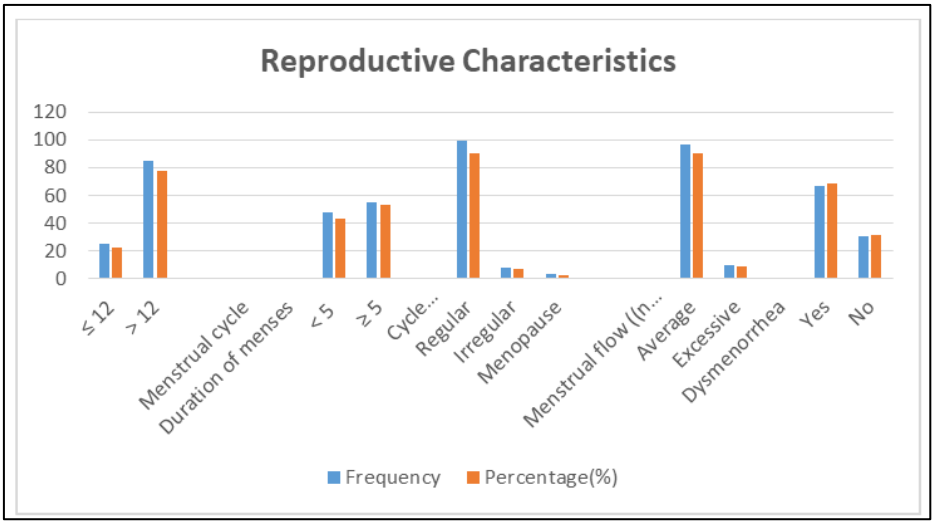

Figure 1: Clinical characteristics of the study subjects (n = 110)

Table 2: Findings on colposcopic examination of cervix (n =110)

Variable	Frequency	Percentage (%)
SCJ		
Satisfactory (seen clearly)	100	90.9
Unsatisfactory	10	9.1
Acetowhite		
Yes	102	92.7
No	8	7.3
Density of acetowhite area		
Light	56	54.9
Dense	46	45.1
Punctuation		
Yes	43	39.1
No	67	60.9
Mosaicism		
Yes	32	29.1
No	78	70.9

Colposcopic evaluation shows that squamo-columnar junction (SCJ) was seen clearly in > 90% cases. Visual inspection with acetic acid (VIA) positivity was considered if there were acetowhite areas in the transitional zone close to squamocolumnar junction (SCJ). Out of total 110 patients, 102(92.7%) exhibited

acetowhite area; of them about 55% exhibited light acetowhite SCJ and the rest had dense acetowhite areas. Nearly 40% had punctuation and 29.1% exhibited mosaic appearance.

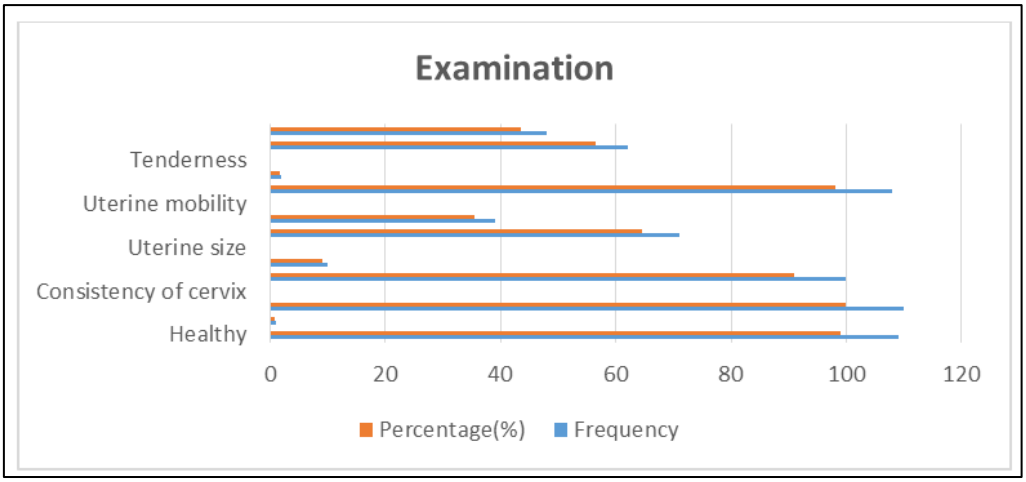

Figure 2: Findings of vagina, cervix and uterus on examination

Table 3: Distribution of patients by colposcopic diagnosis

Variable	Frequency	Percentage (%)
Colposcopic result (n = 110)		
Positive (CIN)	88	80.0
Negative (Cervicitis or Normal)	22	20.0
Colposcopic Grading (n = 88)		
CIN-1	44	50.0
CIN-2	26	29.5
CIN-3	18	20.5

Colposcopic evaluation demonstrates that 88(80%) had positive lesions (CIN) and the rest 22(20%) had negative lesion (cervicitis or normal). Half (50%) of the colposcopically positive lesions were graded as CIN-1, 29.5% as CIN-2, and 20.5% as CIN-3.

Table 4: Patients stratified by histopathological finding of cervical biopsy

Variable	Frequency	Percentage (%)
Comment (n = 110)		
*Positive (CIN)	49	44.5
**Negative (Cervicitis or normal)	61	55.5
Grading (n = 49)		
CIN-1	18	36.7
CIN-2	17	34.7
CIN-3	6	12.2
Carcinoma in situ	3	6.2
Squamous cell carcinoma	5	10.2

Of the 110 patients, 49(44.5%) were histopathologically confirmed as having cervical intraepithelial neoplasia (CIN) or dysplasia as revealed by examination of colposcopically-guided biopsy material taken from the cervix. Of them, 36.7% had CIN-1, 34.7% had CIN-2, 12.2% CIN-3, 10.2% had invasive squamous-celled carcinoma and the rest (6.2%) had carcinoma in situ.

Table 5: Accuracy of colposcopy in diagnosing CIN

Colposcopic findings	Histology of cervical biopsy		Total
	CIN Present	CIN absent	
CIN	41	47	**88**
Cervicitis or normal	8	14	**22**
Total	**49**	**61**	**110**

The accuracy of colposcopy in diagnosing cervical intraepithelial neoplasia (CIN) is shown in Table VII. The test's sensitivity in diagnosing CIN was 41/49(100 = 83.7%), and the test's specificity in correctly detecting those who did not have CIN was 14/61 (100 =23.0%). The positive and negative predictive values of the test were 41/88 × 100 = 46.6% and 14/22 × 100 = 63.6% respectively, while the percentages of false positives and false negatives were 47/88 × 100 = 53.4% and 8/22 × 100 = 36.4% respectively. The overall diagnostic accuracy was (41+14)/(41+47+8+14) × 100 = 55%.

Table 6: Accuracy of colposcopy in differentiating high-grade from low-grade CINs

Colposcopic Grading	Histological grading of CIN		Total
	High-grade*	Low-grade**	
High-grade	24	20	**44**
Low-grade	2	42	**44**
Total	26	62	88

The sensitivity of the colposcopy in differentiating high-grade CIN from the low-grade lesions was 24/26 × 100 = 92.3% and the test's specificity in correctly detecting those who had low-grade (CIN) lesions was 42/62 × 100 = 67.7%. The positive and negative predictive values of the test in differentiating high-grade from low-grade lesions were 24/44 × 100 = 54.5% and 42/44 × 100 = 95.5%, respectively, while the percentages of false positives and false negatives were 20/44 × 100 = 45.5% and 2/44 × 100 = 4.5% respectively. The overall diagnostic accuracy in differentiating high-grade cervical lesions from the low-grade ones was (24+42)/(24+20+2+42) × 100 = 75.0%.

DISCUSSION

Cervical cancer prevention strategies in developed countries traditionally rely on cytology screening followed by the treatment of high-grade cervical intraepithelial neoplasia (CIN2+), a precursor to cervical cancer. However, cytologic screening alone often falls short in accurately identifying women with cancer precursors, leading to over-treatment of many who may not require it. To address this, colposcopy has been introduced as a supplementary test to identify better those needing treatment. Colposcopy needs to enhance specificity while maintaining sensitivity for optimal use [10].

In this study, colposcopic evaluation revealed that 80% of the participants exhibited positive lesions (CIN), while 20% showed negative findings (normal cervix or cervicitis). Among the colposcopically positive cases, 50% were classified as CIN-1, 29.5% as CIN-2, and 20.5% as CIN-3. However, when colposcopically directed biopsies were subjected to histopathological evaluation, only 44.5% were confirmed to have cervical intraepithelial neoplasia (CIN) or dysplasia, with varying grades. This study highlighted a trend of over-diagnosis of CIN through colposcopy.

Comparisons with previous research, such as the study by Maziah and colleagues in 1991, revealed significant variability in the accuracy of colposcopy. While Maziah's study reported a much higher accuracy rate for colposcopy (94%), it also identified an alarming underdiagnosis of CIN-III and the complete escape of micro-invasive carcinoma through colposcopy. These inconsistencies are often attributed to the subjective and operator-dependent nature of specific diagnosis in colposcopy [11].

Despite the reasonably high sensitivity of colposcopy in diagnosing CIN (83.7%) observed in this study, its specificity was strikingly low (23%). This means that while colposcopy is sensitive in detecting CIN among those with the disease, it struggles to correctly rule out CIN in those without the disease, leading to many false CIN diagnoses. This situation subjects patients to unnecessary follow-up evaluations, costs, and emotional distress. The overall diagnostic accuracy of the colposcope for diagnosing CIN and cervicitis was low (55%), with a positive predictive value of 46.6%.

The accuracy of colposcopy has been a matter of increasing scrutiny. Various studies have reported a wide range of sensitivity (30–99%) and specificity (39–92%) for colposcopy in diagnosing high-grade CIN (CIN2+). Recent, higher-quality studies have reported more modest sensitivity (56–60%) and positive predictive values (60%). The variability in colposcopy performance can be attributed to disease prevalence and operator training [12].

In the study, colposcopy's effectiveness in diagnosing CIN can vary significantly, influenced by factors like operator skill and disease prevalence. While colposcopy may excel in differentiating high-grade CIN from low-grade lesions, its overall diagnostic accuracy and specificity can be suboptimal. Striking the right balance between sensitivity and specificity is crucial for effective cervical cancer prevention programs that aim to identify and treat high-risk cases while avoiding unnecessary interventions for those with low-grade or no disease. Ongoing research and improvements in colposcopy techniques and operator training may enhance its role in cervical cancer prevention.

CONCLUSION

Based on the study's findings, it can be concluded that colposcopy is an optimally sensitive tool to diagnose CIN. Still, its specificity in correctly excluding those with normal cervix or cervicitis is inappreciably low with overall diagnostic accuracy. However, it is highly sensitive to differentiate high-grade CIN (CIN2+) and carcinoma in situ from the low-grade lesions. Its specificity in correctly differentiating low-grade CIN lesions is moderate.

RECOMMENDATIONS

- Paps smear test positive patients or Paps test persistently showing inflammatory changes but does not respond to adequate recommended therapy, if sent to further evaluation by colposcopy, may improve the yield of both sensitivity and specificity.
- A large-scale study should be conducted to validate the present study's findings.

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