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Review Article

From diagnosis to treatment: a holistic approach to intraepithelial cervical disease

Sumedha Gupta[1]*, Dheer Singh Kalwaniya[2]

[1]Department of Obstetrics and Gynaecology, VMMC and SJH, New Delhi, India
[2]Department of Surgery, VMMC and SJH, New Delhi, India

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***Correspondence:**
Dr. Sumedha Gupta,
E-mail: sumedhagupta91@gmail.com

ABSTRACT

Cervical cancer remains a significant cause of mortality among women worldwide. Screening methods play a crucial role in identifying individuals with cervical pre-cancerous lesions, allowing for timely intervention to prevent progression to invasive disease. Treatment modalities for cervical intraepithelial neoplasia (CIN) are effective, straightforward, and safe. The choice between ablative techniques (such as cryotherapy or thermal ablation) and excisional techniques (like large loop excision or cold knife conization) depends on lesion characteristics and transformation zone type. Ablative techniques are particularly suitable for low-resource settings due to their simplicity, low complication rates, and cost-effectiveness. In areas where access to colposcopy and histopathology services is limited, strategies such as visual inspection with acetic acid (VIA) followed by immediate ablative treatment for VIA-positive individuals are recommended by the World Health Organization. This approach not only prevents the progression of high-grade CIN but also ensures high compliance among screen-positive individuals. Overall, effective screening and treatment strategies are essential in reducing the burden of cervical preinvasive lesions and preventing the development of cervical cancer.

Keywords: Intraepithelial cervical disease, Cervical dysplasia, Cervical screening, Excision techniques, Ablative techniques, Thermal ablation, VIA, Low resource settings

INTRODUCTION

Intraepithelial lesions of the cervix are characterized by the presence of abnormal cells confined within the surface layers of these epithelial tissues. These conditions, collectively known as intraepithelial neoplasia, are predominantly caused by persistent infection with certain types of human papillomavirus (HPV), although other factors such as immunosuppression and hormonal influences may also play a role. These diseases are of significant clinical importance due to their potential to progress to invasive cancer if left untreated. Early detection and management are essential for preventing the development of invasive malignancies and reducing associated morbidity and mortality rates. Screening programs utilizing cytology (Pap smear), HPV testing, and colposcopy have been instrumental in identifying precursor lesions and guiding appropriate interventions.[1] This aims to provide a comprehensive overview of intraepithelial diseases affecting the cervix including its etiology, epidemiology, clinical presentation, diagnostic modalities, management strategies, and implications for patient care. By enhancing understanding of these conditions, healthcare providers can optimize their approach to prevention, diagnosis, and treatment, ultimately improving outcomes for individuals at risk of or affected by intraepithelial neoplasia.

CERVICAL PREINVASIVE LESION

Cervical cancer is highly preventable through effective screening programs detecting precursor conditions. High coverage and compliance can reduce incidence by up to 80%.[1] Point-of-care tests like VIA and rapid HPV detection enable screening and treatment in 1 visit, crucial in low and medium-income countries with limited resources, WHO recommends screening women aged 30-49 with VIA or HPV, followed by timely treatment.[2]

HISTORY OF EVOLUTION OF TERMINOLOGY

In the early 20th century, Schauenstein, Schottländer, and Kermauner's studies led to the introduction of "carcinoma *in situ*" (CIS) by Broders in 1932, marking a pivotal moment in recognizing precancerous lesions. Reagan coined "dysplasia" in 1953 to describe atypical epithelial differentiation, while Koss suggested in 1963 that all cervical dysplasias could progress to invasion, a theory later disproved. Richart's 1968 CIN terminology classified lesions into three groups, further refined in 1990 to distinguish low-grade (LSIL) and high-grade (HSIL) lesions (Table 1). Helper and Friedell introduced "adenocarcinoma in situ" (AIS) and associated diagnostic criteria, laying the groundwork for understanding precursor lesions of invasive adenocarcinoma.[3]

CURRENT WHO CLASSIFICATION

The current WHO classification of cervical squamous epithelium precancerous lesions is based on HPV-related carcinogenesis. Transforming HPV infections, associated with high-risk genotypes, lead to neoplastic transformation via E6 and E7 oncogenes. This results in HSIL (CIN 2/3) characterized by p16 overexpression and a significant risk of progression to invasive carcinoma. Permissive HPV infections, in contrast, typically cause LSIL (CIN 1) with focal p16 staining, often resolving within 1 to 2 years. AIS serves as a precursor lesion for mucinous adenocarcinoma, with significant progression risk. Low-grade lesions in cervical columnar epithelium lack classification due to unclear HPV involvement.[3]

NATURAL HISTORY OF CERVICAL PREMALIGNANT LESIONS

HPV infection is a critical precursor to cervical cancer, affecting about 90% of cases, including both squamous cell carcinoma (SCC) and adenocarcinoma. Persistent infection with oncogenic HPV types, primarily targeting basal cervical epithelial cells, disrupts normal cell cycle control through viral oncoproteins E6 and E7. This leads to progressive cellular changes termed CIN, categorized into CIN 1, 2, and 3 based on severity. While most CIN 1 lesions regress, some progress to higher grades and potentially invasive cancer (Table 2). Notably, CIN 3 exhibits a significant risk of progression to invasive cancer if left untreated.[4] Adenocarcinoma, comprising about 10% of cervical cancers, originates from AIS or glandular lesions, often multifocal and associated with oncogenic HPV infection.[5,6]

Table 1: Cervical preinvasive lesion evolution of terminology.

2014 WHO classification	2003 WHO classification	Synonyms
Low-grade squamous intraepithelial lesions	CIN 1	Mild dysplasia
High-grade squamous intraepithelial lesion cytology	CIN2 CIN3	Moderate dysplasia, severe dysplasia

Table 2: Natural history of CIN lesions.[4]

Preinvasive lesion	Regression (%)	Persistence (%)	Progression to CIS (%)	Progression to invasion (%)
CIN 1	57	32	11	1
CIN 2	43	35	22	5
CIN 3	32	< 56	-	> 12

RISK FACTORS FOR CERVICAL PREMALIGNANT LESIONS

Cervical cancer risk factors include age, behavioural factors like early sexual activity, multiple sexual partners and tobacco use, oral contraceptive use, DES exposure, increasing parity, immunosuppression, and inadequate screening, particularly among socioeconomically disadvantaged women.

SCREENING MODALITY

The three main screening modalities for cervical cancer are HPV testing, cytology, and VIA. HPV testing is the most sensitive method but may not be widely available and is recommended for women over 30 using validated tests such as hybrid capture 2 or Cobas, Xpert, Cervista, APTIMA etc. Cytology remains an option for centres with established programs, while VIA is suitable for limited resource settings. Co-testing with cytology and

HPV may be considered, but the benefit is small compared to HPV testing alone. Cytology, available in most urban areas and tertiary hospitals, has high specificity but low sensitivity (60-70%), requiring frequent testing. Liquid-based cytology (LBC) does not improve sensitivity but reduces unsatisfactory smears and allows HPV testing from the same sample.[7] Centres with quality cytology programs may continue, while others may consider switching to primary HPV screening or supplementing with VIA, which has comparable sensitivity but lower specificity. However, VIA may require more colposcopy referrals due to false positives. In low-resource settings, VIA remains a viable option, but affordable HPV testing may change this in the future. A colposcopy-guided biopsy is preferred for diagnosis, but VIA can guide biopsy if colposcopy is unavailable. Linking screening with treatment, especially through the single-visit approach (SVA), reduces loss to follow-up.[8] The 'see-and-treat' approach allows immediate treatment for high-grade abnormalities on cytology or abnormal colposcopy without histopathological confirmation. Similarly, 'screen-and-treat' strategies, using cryotherapy or thermal ablation based on abnormal HPV tests or VIA, are effective in low-resource settings without colposcopy facilities, minimizing untreated CIN lesions while accepting a risk of over-treatment.[9]

AGE OF SCREENING

In optimizing cost-effectiveness, the initiation and cessation of cervical cancer screening are determined by age-specific cancer burden. In India, where cervical cancer incidence is extremely low below age 25, screening initiation before this age is not recommended for asymptomatic women, irrespective of sexual activity onset. Limited resource settings should initiate screening after age 30, targeting a single round between ages 35-40 years if resources permit (Table 3). Ceasing screening for women over 65 with prior adequate negative screenings and no CIN2+ history within 20 years is advised. Adequate prior screening entails three consecutive negative cytology or two consecutive negative co-tests within 10 years, with the last test within 5 years.[10] For women with a history of hysterectomy due to CIN2+ lesions, screening should continue for 20 years post-surgery, while those with hysterectomy for benign conditions need not continue screening. The government of India recommends VIA screening every 5 years from age 30 to 65. However, accuracy decreases in postmenopausal women due to changes in the transformation zone. Other guidelines suggest screening at least once to three times until age 50. In India, a single round of VIA screening reduced cervical cancer incidence by 30% and mortality by 42%, with the greatest impact observed in women aged 30-39.[11] Another study showed a 25-31% reduction in lifetime risk of invasive cervical cancer with VIA and a 30-36% reduction with HPV DNA testing at age 35. Two screenings at ages 35 and 40 reduced lifetime risk by 40%.[12]

Table 3: Resource-based cervical cancer screening.

Variables	Good resource settings	Limited resource settings
Target age group	25-65 years	30-65 years (In post-menopausal women, screening with VIA may not be as effective)
Age to start (years)	Cytology at 25 years, Primary HPV testing/co-testing at 30 years	VIA at 30 years
Frequency	Primary HPV testing or co-testing-every 5 years, Cytology alone-every 3 years	Every 5 years
Follow-up after treatment	HPV testing (preferred) or cytology or colposcopy, 12 months	VIA, 12 months

SCREENING METHODS

Cytology as primary screening modality

Cytology-based programs have significantly decreased the incidence of cervical cancer in developed nations. While a single Pap test demonstrates moderate sensitivity (51%-53%) for detecting CIN2/3, its specificity is notably high at 96.3%. As a result, cytology is currently most effectively utilized as a triage tool for HPV-positive cases, aiming to minimize unnecessary colposcopies.[13]

Primary HPV testing

Primary HPV testing has replaced cytology in cervical cancer screening programs in several countries, such as Australia and parts of Europe. While initial rounds of screening with HPV testing show higher detection rates of high-grade precancerous lesions compared to cytology, subsequent rounds may show similar or lower rates. HPV testing provides better reassurance of the current absence of high-grade lesions, allowing for extended screening intervals of 5 or even 10 years.[14,15] However, the specificity and positive predictive value of HPV testing are low, necessitating triage with additional tests such as cytology or VIA to reduce unnecessary referrals to colposcopy (Figure 1-3). In resource-rich settings, screening every 5 years with an approved HPV test or co-test is recommended. In settings where genotyping or quality cytology is unavailable, VIA may serve as a feasible option to triage HPV-positive cases, as per FOGSI good clinical practice recommendations.[13]

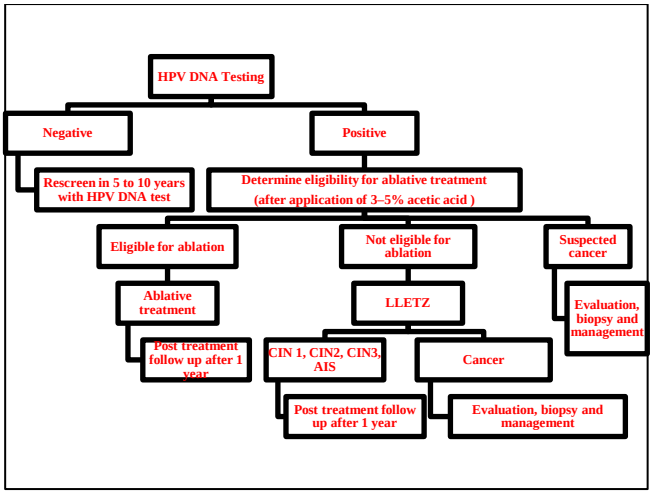

Figure 1: Primary HPV DNA test screening (screen-and-treat approach).

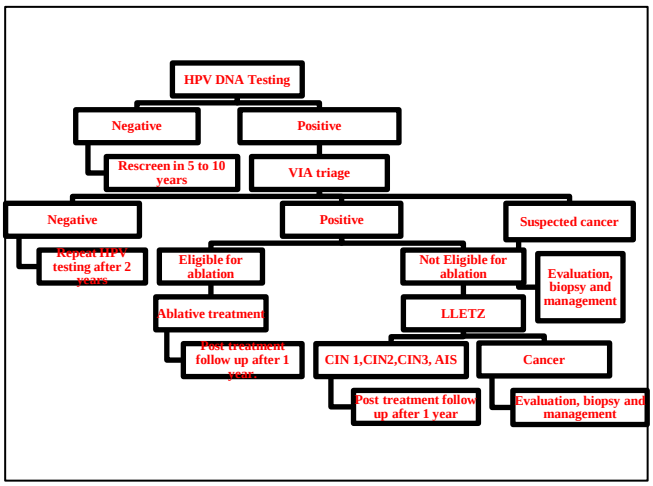

Figure 2: Primary HPV screening and via triage followed by colposcopy (screen, triage and treat approach).

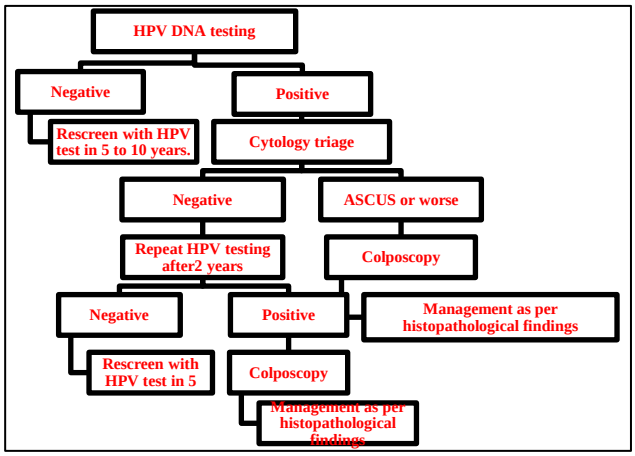

Figure 3: Primary HPV screening and cytology triage followed by colposcopy (screen, triage and treat approach).

Co-testing with HPV testing and cytology

In India, the combination of highly sensitive validated HPV testing with highly specific cytology every 5 years is the most effective screening modality (Figure 4). Co-testing detects 51% more cases of CIN2/3 or invasive cancer than cytology alone.[16] Schiffman et al found that the first co-test could detect 67.9% of cases likely to progress in the next 10 years. While only a small fraction of cases benefits from adding cytology to HPV testing (3.5% preinvasive and 5.9% invasive disease), considering the infrequency of screening in India, co-testing is prudent, despite its cost.[8]

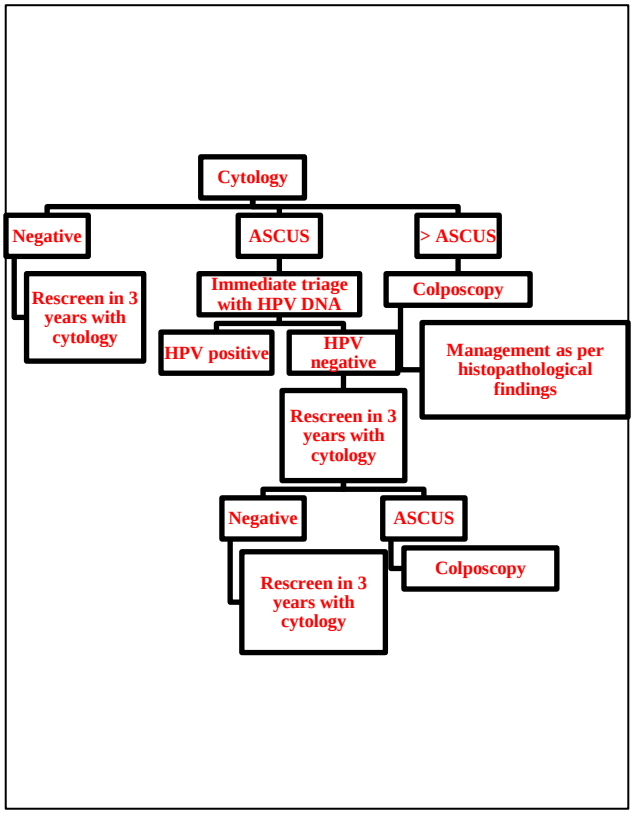

Figure 4: Primary cytology screening and colposcopy triage (screen, triage and treat approach).

VIA as the primary screening modality

VIA stands out as a promising screening tool in low-resource settings owing to its cost-effectiveness and minimal follow-up loss (Figure 5).[17,18] The combined sensitivity and specificity of VIA in detecting CIN grade 2 or higher (CIN2+) range from 16% to 82.6% and 82.1% to 96.8%, respectively [10]. When compared to cytology, VIA exhibits superior sensitivity (90% vs. 50%) but lower specificity (37% vs. 93.5%), resulting in an increased burden of false-positive cases.[18,19] VIA facilitates Same Visit Approach (SVA) screening in LMICs due to its instantaneous results and seamless linkage with treatment.[20] VIA-positive cases can undergo either colposcopy and biopsy or immediate treatment with ablation, contingent upon meeting specific criteria.

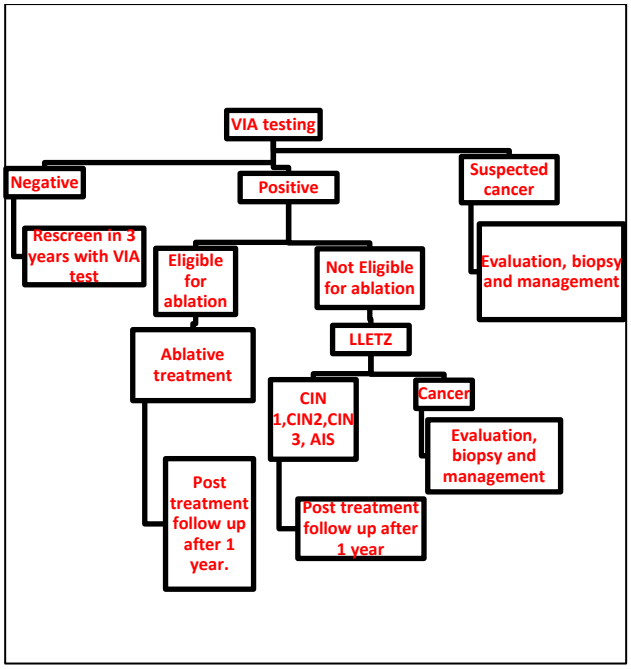

Figure 5: Primary via screening (screen-and-treat approach).

COLPOSCOPY

Colposcopy, employing magnification and robust illumination, is a diagnostic cornerstone for assessing the cervix, vagina, and vulva. By applying a 3% to 5% solution of acetic acid, cellular characteristics, especially high-grade lesions, are highlighted through the "acetowhite" effect. Initial examination at low magnification provides an overall impression, while higher magnification aids in characterizing lesions, particularly in discerning vascular patterns. Utilizing a green-light filter enhances the visualization of vessels. Key objectives of colposcopic assessment include confirming cytologically detected lesions, defining lesion characteristics to exclude occult micro invasion, assessing lesion extent across endo- and ectocervix, and guiding biopsy site selection for histologic confirmation. Adequate colposcopy ensures comprehensive visualization of the squamocolumnar junction.

NORMAL COLPOSCOPY

In a normal cervix, the ectocervix is lined with smooth, pink squamous epithelium, while the endocervix is lined with single-layered, mucin-secreting columnar epithelium with glands. Healthy squamous epithelium remains unaffected by acetic acid but stains brown with Lugol's iodine, while healthy columnar epithelium exhibits a grape-like appearance post-acetic acid application and remains unstained with Lugol's iodine. The transformation zone (TZ), where metaplasia occurs from columnar to squamous epithelium, displays different staining patterns with acetic acid and Lugol's iodine. Dysplastic lesions, often found at the squamous-columnar junction, are distinct from surrounding healthy tissue. In menopausal women, the transformation zone may recede into the endocervical canal, leading to an unsatisfactory colposcopy.

ABNORMAL COLPOSCOPIC FEATURES

After applying a 3% to 5% acetic acid solution, increased nuclear density results in white areas, indicating various conditions including immature metaplastic epithelium, HPV infection, and cervical neoplasia. In high-grade dysplasia or intraepithelial neoplasia, the acetowhite reaction is faster, more intense, and persistent. Lesion severity correlates with sharp demarcation, increased vascularity, and dense aceto-whitening. Punctation and mosaic patterns characterize neovascularization. Fine punctation suggests low-grade CIN, while coarse punctation indicates high-grade CIN. Mosaic patterns, appearing partitioned, also reflect lesion severity, with irregular patterns associated with high-grade CIN.

Lugol's iodine stains mature squamous epithelium dark-brown due to its glycogen content, contrasting with immature metaplasia, CIN, or atrophic epithelium, which lack glycogen and appear iodine-negative. A speckled appearance with iodine indicates immature metaplasia or low-grade CIN, while a yellow stain suggests high-grade CIN. Atypical vessels, such as comma or corkscrew shapes, hint at invasion, along with irregular epithelial surfaces, intense aceto-whiting, and irregular punctation and mosaic patterns. Colposcopy, while complementary to cytology, can both overcall and under-call lesions, necessitating thorough training and ongoing quality control through histology correlation.

MANAGEMENT

Atypical squamous cells with undetermined significance

Atypical squamous cells of undetermined significance (ASCUS) cytology is observed in approximately 2.8% of women aged 30 to 64 years, with up to 23–-74% testing positive for HPV. The ASCUS/LSIL triage study (ALTS) evaluated different triage approaches for ASCUS cytology, including reflex HPV testing, repeat cytology at 6 months, or immediate colposcopy. It found that HPV triage detected the highest cumulative cases of CIN3+ (72.3%), followed by conservative management (5%), and immediate colposcopy (54.6%). Notably, HPV triage demonstrated a sensitivity of 92.4% for detecting CIN3 cases, making it as effective as immediate colposcopy while reducing unnecessary referrals.[21] For women aged 3-64 years with ASCUS, HPV testing is preferred for triage; if unavailable, repeat cytology at 1 year is recommended.[22] For women ≤30 years with ASCUS or LSIL, annual cytology for 2 years is advised. However, where compliance is an issue or HPV testing is not feasible, colposcopy/VIA with directed biopsy is an acceptable alternative for all age groups.

Low-grade squamous intraepithelial lesions

In the ALTS trial, 1572 women with LSIL were monitored with either colposcopy, HPV testing, or repeat cytology at 6 months. With over 80% testing positive for HPV, HPV triage was largely unnecessary for women with LSIL. Therefore, colposcopy is the preferred management approach for LSIL cytology. In cases where colposcopy is unavailable or cytology accuracy is uncertain, HPV testing may serve as a triage method. For issues related to compliance, the 'See-and-Treat' approach is acceptable. However, colposcopy and treatment may pose more risks than benefits for women under 30 due to higher regression rates (70% with CIN2) and lower progression rates (0.5% with CIN3).[21] Thus, colposcopy should be reserved for severe/persistent cytology results. Immediate colposcopy is also favoured for post-menopausal women. Nonetheless, ensuring clear delineation of the transformation zone (TZ) with an endocervical speculum is highly recommended due to the likelihood of TZ regression.

ASC-H and high-grade squamous intraepithelial lesion cytology

HPV triage is discouraged due to high HPV positivity rates (65.8% for ASC-H and 89-97% for HSIL), which typically warrant immediate colposcopy with endocervical evaluation. If the transformation zone (TZ) is not visualized, a diagnostic excisional procedure is preferred, except during pregnancy. In non-compliant cases, the single visit approach (SVA) with cervical ablation is acceptable if criteria are met, although without a diagnostic specimen. For younger women with normal colposcopy and type-I TZ after a high-grade smear, regular follow-up is emphasized, with a diagnostic excisional procedure recommended if an abnormal screening test persists for 2 years.[23]

Glandular cell abnormalities

Approximately 30% of women aged over 40 with atypical glandular cytology are at risk of preinvasive or invasive diseases. While most of these lesions are squamous, it's crucial to note the probabilities of detecting other malignancies: endometrial malignancy stands at 2-3%, cervical AIS at 3-4%, invasive adenocarcinoma cervix at 2%, and cervical SCC at 1%.[24] Hence, a comprehensive evaluation is imperative to exclude endometrial, ovarian, or cervical malignancy (Figure 6). Women exhibiting atypical glandular cells, irrespective of the sub-categories, necessitate thorough assessment including colposcopy, directed biopsy, and endocervical sampling.[24]

Screening in HIV-infected women

HIV infection significantly elevates the risk of cervical cancer development, with approximately 10% of HIV-positive women experiencing CIN2+ annually, compared to 1-2% in HIV-negative counterparts. The prevalence of invasive cervical cancer and CIN2+ lesions among HIV-positive women is notably higher, underscoring the importance of early screening upon HIV diagnosis. Consistent with WHO and ASCO recommendations, screening frequency for HIV-positive women should be doubled compared to the general population. Integration of antiretroviral therapy (ART) services with cervical cancer screening programs is essential. Positive screening cases should be managed in alignment with standard protocols for the general population.[25-27]

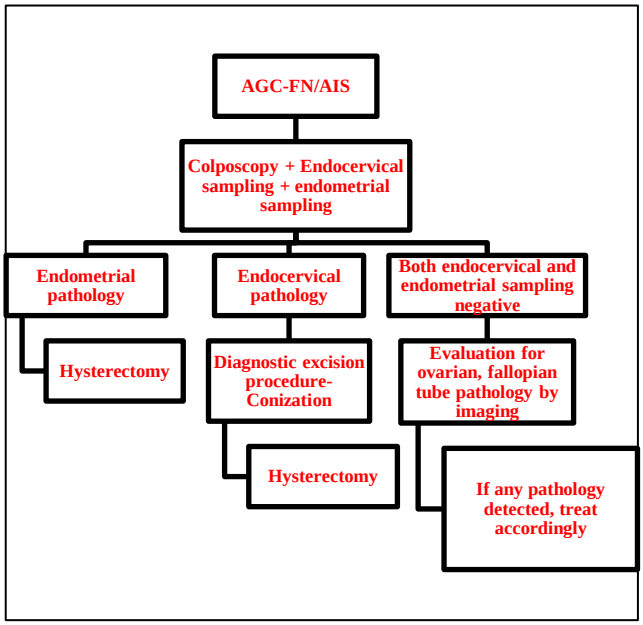

Figure 6: Management of atypical glandular cell-favouring neoplasia, AIS.

PRINCIPLES AND TECHNIQUE OF TREATING CIN

HSIL should be promptly treated except during pregnancy. CIN 1 lesions typically require no treatment unless persistent beyond two years or showing signs of progression. CIN 2 lesions with p16INK4 overexpression require immediate treatment; otherwise, follow-up is recommended.[28] Treatment must address the entire transformation zone, extending to a depth of at least 5 mm to eradicate high-grade lesions effectively. CIN can be treated with ablative techniques, such as cryotherapy or thermal ablation, destroying the epithelium up to a depth of 6 to 7 mm.[29]

Alternatively, excision methods like LLETZ or CKC remove the transformation zone. Ablative techniques are simpler and safer, suitable for LMICs, increasing access to care. Cryotherapy is cost-effective, but LLETZ offers improved efficacy at a higher cost. A punch biopsy before ablative treatment aids in histopathological diagnosis. Hysterectomy is not typically recommended for CIN treatment.[30]

CRYOTHERAPY

Nitrous oxide (N_2O) or carbon dioxide (CO_2) exhibits rapid freezing properties, reaching temperatures as low as minus 60 or 80 degrees Celsius under atmospheric pressure when compressed. This characteristic of refrigerant gases forms the basis of cryotherapy procedures. Through a controlled process, the gas is directed through a nozzle to the metallic probe's tip, which is then applied to the cervix's transformation zone. By lowering the temperature of the underlying cervical epithelium to approximately minus 20 degrees Celsius, intracellular water crystallizes, leading to the coagulation of cellular proteins. It induces cryo-necrosis of CIN lesions. Eligibility criteria include type I transformation zone, lesion limited to ectocervix (<75%), and absence of invasive cancer. The outpatient procedure, performed without anaesthesia, involves applying a probe to the cervix, freezing for three minutes, thawing for five, and then freezing again. Follow-up is advised after 6 to 12 months. Cryotherapy can be performed based on colposcopy findings or even on HPV-positive women, preceded by an acetic acid application for eligibility confirmation. Sauvaget et al. meta-analysis of 11 RCTs showed cryotherapy's efficacy with a 92% cure rate for CIN 2 and 85% for CIN 3 lesions.[31] In Peru, primary care settings achieved a 70% cure rate for CIN 3 lesions in one year. Though cryotherapy's recurrence rate is higher than LLETZ, it offers fewer major complications and obstetric risks. WHO recommends cryotherapy, particularly in resource-limited settings, for its simplicity and effectiveness. However, logistical challenges such as cost and availability of refrigerant gas hinder widespread adoption. Innovations like CryoPen© and CryoPop©, which eliminate the need for refrigerant gas and are portable, aim to address these barriers.[32]

THERMAL ABLATION

Thermal ablation, utilizing heat to coagulate cervical epithelium, offers a simple, minimally painful procedure with low complication rates. The portable equipment is electrically operated or rechargeable battery version applies a heated probe to the cervix for 20 to 45 seconds, effectively destroying epithelial tissue. Patient selection criteria are similar to those for cryotherapy, ensuring suitability. Extensively used by Gordon and Duncan, with a success rate of 95% at one year and 92% at five years, thermal ablation demonstrates high efficacy in curing CIN lesions, as evidenced by Dolman et al meta-analysis and studies in HIV-positive women.[33]

LARGE LOOP EXCISION OF TRANSFORMATION ZONE

LLETZ, or loop electrosurgical excision procedure (LEEP), is highly effective for treating all grades of CIN, first demonstrated by Walter Prendiville in 1986. Using a loop electrode powered by an electrosurgical unit, it excises a cone-shaped sample from the cervix, typically under local anaesthesia as an outpatient procedure. The excised tissue is sent for histopathologic evaluation. Cure rates exceed 90% for CIN 2/CIN 3 lesions, but complications, including bleeding (7-10%) and cervical incompetence (risk of 1 in 143 women for preterm delivery), can occur.[34] Other rare complications include purulent vaginal discharge, pelvic pain, and cervical stenosis. Careful consideration of transformation zone type and cone length is crucial to minimize adverse events.[34]

COLD KNIFE CONIZATION

Cervical conization with a scalpel (cold knife conization, CKC) is typically used for AIS and micro-invasive carcinoma due to the need for precise depth control, which is challenging with a loop. CKC offers improved histopathological assessment without thermal artefacts seen in LLETZ. However, it requires regional or general anaesthesia and hospitalization, with higher risks of primary and secondary haemorrhage and adverse pregnancy events compared to LLETZ. Despite these differences, six randomized controlled trials found no disparities in failure rates between LLETZ and CKC for treating CIN.[35]

HYSTERECTOMY

Hysterectomy is not a primary treatment for any grade of CIN due to potential risks, including compromise of treatment outcomes if occult invasive cervical cancer is present. In cases where hysterectomy is indicated for benign conditions, steps should be taken to exclude asymptomatic invasive cervical cancer beforehand. Hysterectomy may be considered for AIS in women who have completed childbearing.

FOLLOW-UP AFTER TREATMENT

After CIN treatment, histopathological review guides further management, with invasive cancer warranting a referral to a tertiary care center for staging. Positive margins post-LLETZ or CKC may necessitate repeat procedures. Regular follow-up is crucial, with initial evaluation at one year and subsequent screenings every 3 to 5 years if disease-free. Annual follow-ups for CIN 3 or AIS are recommended for three years. High-risk HPV testing, with its high sensitivity, is the preferred "test of cure," distinguishing residual disease from cure. A negative HPV test indicates successful treatment.[36-38]

CONCLUSION

Diseases of the cervix, vagina, and vulva, mainly caused by HPV, can progress to invasive cancer if untreated. Early detection via cytology (Pap smear) and HPV testing is crucial for identifying precursor lesions and preventing malignancy. Screening strategies include VIA, cytology, and HPV testing, utilizing single-visit 'see-and-treat' or 'screen-and-treat' methods. Ablative and excisional

treatments are used for cervical lesions. Vulvar SIL involves premalignant lesions requiring biopsy and surveillance to prevent invasive cancer. VaIN, a risk for invasive vaginal cancer, is managed conservatively to preserve vaginal function.

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