Cervical cancers are the most common genital cancers in the developing world and constitute about 20-30% of all female genital cancers in these regions. However, the incidence is lower in the western countries where screening programmes for this cancer was implemented. Worldwide, 500,000 new cases are diagnosed annually. The incidence is around between 6 and 30 per 100,000 women for the invasive and preinvasive diseases, respectively. This chapter will briefly overview the management strategies of the preinvasive cervical lesions.

Cervical intraepithelial neoplasia (CIN) is a premalignant cervical disease and it is also called cervical dysplasia or cervical squamous intraepithelial lesion. CIN consist of a range of histological diagnosis. CIN 1 is used for low grade lesions (lower third of the epithelial lining). CIN 2 is used for high grade lesions (abnormal maturation of the lower two-thirds of the epithelial lining). CIN 3 is also used for high grade lesions but severely atypical cellular changes including more than two-thirds of the epithelial thickness and full thickness lesions. Women with low grade CIN have minimal potential for developing cervical malignancy, while those with high grade lesions are at high risk of progression to malignancy.

**Incidence**

The diagnosis of high grade lesions is common in women between the age of 25 and 35. In the USA, more than 1 million women are diagnosed each year with low-grade cervical intraepithelial lesions (CIN 1), and approximately 500,000 are diagnosed with high-grade cervical intraepithelial lesions (CIN 2-3) (1).

**HPV-CIN**

HPV infection is extremely common and varies with the patient’s age. Women with persistent HPV infections have a higher risk of developing CIN. HPV is the most important independent risk factor for these disorders among sexually active population. The risk of infection increases when the number of sex partners increases. At least 80 percent of sexually active women will have acquired a genital HPV infection by age of 50. Most HPV infections are transient and over 50 percent of new infections are cleared in 6 to 18 months, and 80 to 90 percent will resolve within two to five years (2-3). Although HPV infection is considered necessary for cervical neoplasia; HPV alone is not capable of causing these disorders, thus high grade cervical lesions or cancer are not seen at most of the women who have HPV infection. Many environmental factors and for immunologic influences are related with development of cervical cancer and high grade lesions HPV subtype and persistence are the two major risk factors.

**Subtype:** Low grade lesions are caused by low-risk subtypes like HPV 6 and HPV 11, while high grade lesions, persistence, and progression to invasive cancer seems to be associated with high risk HPV subtypes like HPV 16 and 18.

**Persistence:** The persistence may be associated with duration of HPV infection or HPV subtypes that have high oncogenic risk.

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**Cofactors in Pathogenesis**

**Immunosuppression:** The risk of developing CIN is increased at women who have chronic conditions that require long term immunosuppressive treatment and HIV-infected women.

**Cigarette smoking:** Cigarette smoking and HPV infection have synergistic effects on the development of CIN and cervical cancer.

**Herpes simplex virus and chlamydia:** Although chlamydia, herpes simplex virus (HSV), or other sexually transmitted diseases are not a causative factors, they may demolish host immunity resulting in facilitation of persistence of oncogenic HPV viruses.

**Oral contraceptives:** Long-term use of oral contraceptives has been recognized as a cofactor that increases the risk of cervical carcinoma in women who are HPV positive.

**Others:** Genetic, familial, dietary, and endogenous hormonal factors are not thought to play a role in the development of CIN or cervical cancer for the most part.

**Natural History**

The appropriate management of women with different degrees of CIN can only be possible by understanding natural history of them (Figure 1). The degree of the lesions, patient’s age, HPV type, smoking habits, and patient’s immune competence have certain roles at the course of a specific lesion. Although many of CIN 1 lesions tend to regress, nearly 9-16 % of untreated CIN 1 lesions can be diagnosed as CIN 2/3 after 2 years. The high-grade lesions tend to persist or progress, since progression rates are much highly (22% for CIN 2 and 14% for CIN 3). Thus immediate treatment is generally needed.
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Treatment Modalities

Ablation vs Excision

Ablative and excisional treatments constitute two forms of outpatient surgical treatment of CIN. While ablative methods destroy the affected cervical tissue, excisional modalities remove the affected tissue (4). Ablative methods include cryotherapy, laser ablation, electrosurgery, and cold coagulation. Excisional methods include cold-knife conization, loop electrosurgical excision procedures (LEEP or LLETZ), laser conization, and electrosurgical needle conization. The LEEP, using thin wire loop electrodes and long needle electrode electro-surgical cylindrical excision is the major form of outpatient excisional treatment of CIN (5).

The most frequent of excisional methods are laser cone biopsy or LLETZ. The excisional techniques offer the advantage of obtaining a large specimen for pathological assessment to define the disease as well as the completeness of treatment, and performing commonly under local analgesia. In many clinics, LLETZ has now become the standard of care for cervical premalignant lesions. As it maintains cervical reproductive function, it is suitable for patients who wish to retain their fertility (6).

The main disadvantage of LLETZ is frequently reported cauteryization artifact. This artefact is to be expected since both coagulation as well as cutting occurs during LLETZ. In some cases, this artifact will lead to uncertainty on the part of the histopathologist on the completeness of the excision. Both ablative and excisional modalities have a similar efficacy approximately 90 percent with respect to eliminating CIN and reducing a woman’s risk of future invasive cervical cancer (4). The choice of ablation versus excision is based on many factors, such as severity of disease, morbidity, adverse effects, and cost-effectiveness. Excisional treatment is recommended, when there is suspected glandular or invasive squamous disease or if the patient is not compliant with follow-up. Women are candidates for ablative therapy if they have no suspected glandular or invasive squamous disease and are compliant with follow-up. Indications for excisional therapy are: Suspected microinvasion, unsatisfactory colposcopy (the transformation zone is not fully visualized), lesion extending into the endocervical canal (including CIN 1), endocervical curettage showing CIN or a glandular abnormality, lack of correlation between the cytology and colposcopy/biopsies, suspected adenocarcinoma in situ, recurrence after an ablative or previous excisional procedure.

Hysterectomy

Hysterectomy should not be performed as an initial treatment of CIN. There are, however, some indications for which hysterectomy remains a valid treatment option for CIN. Conization specimen margins that are positive for CIN 2, 3, especially in the setting of completed childbearing and expected poor compliance with follow-up. Another indication is technically difficult a repeat excisional procedure, where the cervix and vagina are scarred in a way.

See and Treat Strategy

See-and-treat protocols are performed in an office excisional procedure in at-risk populations based upon findings at colposcopy, rather than having the patient await biopsy results and make a return visit. This approach is an attempt to lower the 20 to 40 percent loss-to-follow-up rate with the traditional multi-visit management of CIN (7). The effectiveness of see-and-treat depends on accurate colposcopy. The main disadvantage of this practice is citing high false positive colposcopy rates resulting in over-treatment.

<table>
<thead>
<tr>
<th>Regression</th>
<th>Persistans</th>
<th>Progression to CIN3</th>
<th>Progression to Inv. Cancer</th>
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<tbody>
<tr>
<td>CIN 1</td>
<td>60%</td>
<td>40%</td>
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<tr>
<td>CIN 2</td>
<td>40%</td>
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<td>20%</td>
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<tr>
<td>CIN 3</td>
<td>33%</td>
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Figure 1. Natural history of CIN.

Colposcopic Assesment of CIN

The colposcopic diagnosis of cervical neoplasia depends on four main features: Colour tone and intensity of acetowhitenning, margins and surface contour of acetowhite areas, vascular pattern and iodine staining. There is usually a distinct demarcation between normal and abnormal epithelium. The colposcopic features that differentiate an abnormal transformation zone from the normal include the following: Colour tone of acetowhite areas; surface pattern of acetowhite areas; borderline between acetowhite areas and the rest of the epithelium; vascular features and colour changes after application of iodine. Colposcopy with directed biopsy is described as ‘gold standard’ for the diagnosis of cervical precancer lesions.

Treatment of CIN

The goal of managing women with CIN is to prevent possible progression to invasive cancer while avoiding overtreatment of lesions that are likely to regress. The appropriate management of women with cervical intraepithelial neoplasia is important, because CIN is a relatively common problem, especially in women of reproductive age. Improper management of CIN can increase the risk of cervical cancer or overtreatment may lead to complications. Therapeutic decision depends on considerations such as patient age; parity; desire for fertility, special populations (pregnancy, adolescents), cervical cytology findings, cervical biopsy results, colposcopic impression, prior cytology and treatment history; the likelihood of compliance of follow-up, operator experience, and nonvisualization of the transformation zone.

Östör AG (8)
Other treatments

Several alternative methods for treatment of CIN have been developed, all of which are currently investigational. This includes photodynamic therapy, cyclooxygenase-2 inhibitors, vaccines, environmental alterations, use of topical agents (difluoromethylornithine, all-trans retinoic acid, cidofovir) and oral agents. However, these treatments do not appear to be as effective as excision or ablation and their clinical role remains to be determined.

CIN I

Aggressive treatment is generally not recommended, because a significant number of these lesions spontaneously regress, and progression to CIN 2, 3 or invasive cancer is uncommon (8,9). Since spontaneous regression is observed in most women with CIN I, expectant management is generally preferred for the patient with biopsy-confirmed CIN I (ie, satisfactory colposcopic examination).

Follow-up with HPV DNA testing every 12 months or repeat cervical cytology every 6 to 12 months is recommended for histological diagnosis of CIN I preceded by ASCUS, ASC-H, LSIL, HSIL. Colposcopy is recommended, when HPV DNA test is positive or repeat cytology ≥ASC-US is reported. Return to routine cytological screening is recommended, when HPV test or negative 2 consecutive repeat cytology tests are determined (5).

Treatment (excisional or ablational) or continued follow-up is acceptable for CIN I with satisfactory colposcopy, when CIN 1 persists for at least 2 years. If treatment is planned, ablative or excisional modalities are appropriate. Ablative treatment is reasonable if colposcopy is satisfactory, endocervical sampling (ECC) is negative for glandular or squamous lesions, and treatment is primary. A diagnostic excisional procedure is recommended for CIN I with unsatisfactory colposcopy, if the endocervical sampling contains CIN, or if the patient has been previously treated (5).

A diagnostic excisional procedure, and follow-up with colposcopy and cytology at 6-month intervals for 1 year, or alternatively a review of the cytological, histological, and colposcopic findings is acceptable for CIN 1 preceded by HSIL or atypical AGC-NOS cytology (satisfactory colposcopy, negative endocervical sampling) (5).

In most cases, an excisional procedure provides both definitive diagnosis and treatment. This approach is universally recommended if colposcopy is unsatisfactory or ECC is positive. A diagnostic excisional procedure is recommended for these cases, when unsatisfactory colposcopy or repeat HSIL or AGC-NOS cytological results detected at follow-up. Management decisions of a patient with CIN 1 preceded by high grade cytological abnormalities (HSIL, AGC-NOS) should take into account colposcopic findings, patient age, and her desire for future fertility (5). After 1 year of observation, women with 2 consecutive “negative for intraepithelial lesion or malignancy” results can return to routine cytological screening (5).

CIN II-III

CIN 2 and 3 are high grade lesions. For CIN 3, the estimated spontaneous regression rate is 32-47%, with 12-40% progression rate to invasive cancer if untreated (10,11). Excisional and ablational treatment modalities are acceptable for women with a histological diagnosis of CIN 2, 3 with satisfactory colposcopy, except for some special circumstances. A diagnostic excisional procedure is recommended for recurrent CIN 2, 3 and for women with a histological diagnosis CIN 2, 3 with unsatisfactory colposcopy. Follow-up with sequential cytology and colposcopy or hysterectomy as primary therapy for CIN 2, 3 is not recommended (5). Prior to any therapeutic intervention, an assessment needs to be made as to whether a patient qualifies for ablative therapy or if she requires a more invasive excisional procedure for further diagnostic work-up. The general management of CIN II-III are shown at Figure 2.

Follow-up After Treatment

A number of follow-up protocols have been advocated, such as use of HPV DNA testing, cytology, and different combinations of cytology, endocervical sampling, and colposcopy at various intervals. The main factor affecting the follow-up is margin status.

Clear margins: There is a high rate of cure when the entire lesion has been excised. This was illustrated in studies with long-term follow-up with colposcopy, cytology, and pelvic examination.

Positive margins: Studies have consistently showed that patients with positive margins after an excisional procedure are at significantly higher risk for residual disease (Figures 3-4). Recurrences in women with positive margins can occur years after treatment.

Women who have positive margins on the excised specimen should be informed about the risks and benefits of
observation versus further treatment, taking into account age, fertility desire, and management preferences.

Clinical follow-up with cytology and endocervical sampling at four to six months, instead of immediate retreatment, is appropriate in patients who are compliant with frequent monitoring. Repeat diagnostic excisional procedure or reevaluation by using cytology with endocervical sampling at 4-6 months after treatment is preferred, when CIN 2, 3 is identified at the margins of a diagnostic excisional procedure or in an endocervical sample obtained immediately after the procedure (5).

HPV DNA testing at 6-12 months, cytology alone or a cytology and colposcopy at 6 month intervals are acceptable options for women with CIN 2, 3 of follow-up after treatment. Colposcopy with endocervical sampling is recommended, when positive HPV DNA or ≥ASCUS detected at repeat cytology result. Routine screening (for at least 20 years commencing at 12 months) is recommended for negative HPV DNA or negative 2 consecutive repeat cytology tests (5).

Hysterectomy is acceptable, when repeat diagnostic procedure is not feasible or recurrent or persistent CIN 2, 3 is diagnosed (5).

Special Populations

**Adolescents:** Annual cytological assessment follow-up is recommended for adolescents with CIN I, ≥HSIL at the 12 month follow-up or ≥ASC-US at the 24 month follow-up should be referred to colposcopy. Follow-up with HPV DNA testing is not recommended. In adolescents with a histological diagnosis of CIN 2, 3 acceptable treatment methods are observation for up to 24 months using both colposcopy and cytology at 6 month intervals (preferred) or treatment, when colposcopy is satisfactory. Treatment is recommended, when a histological diagnosis of CIN 3 with unsatisfactory colposcopy or if CIN 2, 3 persists for 24 months. Adolescents can return to routine cytological screening, when after 2 consecutive "negative for intraepithelial lesion or malignancy" results with normal colposcopy are determined (5).

**Pregnancy:** Follow-up without treatment is recommended for pregnant women with a histological diagnosis of CIN I.

In pregnant women with a histological diagnosis of CIN 2, 3 (absence of invasive disease), additional colposcopic and cytological examinations are recommended. Treatment is not recommended unless invasive cancer is identified. Cytologic and colposcopic reevaluation is recommended within postpartum 6 weeks (5).

**Posttreatment Follow-up of CIN**

The treatment failure rate for CIN has varied between 5-15% and a systematic review could not find a significant difference for the different modalities indicated a systematic review (12). A number of follow-up protocols (cytology, colposcopy, combinations of cytology and colposcopy, and HPV-DNA testing) have been recommended at a variety of intervals (13).

Follow-Up After Treatment:

- Physical examination
- Each 6 months in the first two years
- Annually for the next three years
- Pap test in each visit and colposcopy if needed.
- Avoid smoking
- Give information for vaccines
- Suggest barrier contraception
- Increase folic acid, vitamin C and E, carotene in the diet

**Adenocarcinoma in Situ (AIS)**

AIS is much less commonly encountered compared to CIN 2, 3. Management AIS is both challenging and controversial, due to of minimal colposcopic changes, difficult complete excision, and multifocality with skin lesions. In women who completed child-bearing, hysterectomy continues to be the treatment of choice, while an excisional procedure (conservative management) is preferred for women who wish to maintain their fertility. Margin status is one of the most clinically useful predictors of residual disease. Long term follow-up is recommended for women who do not undergo hysterectomy (5).

Factors Related with Treatment Failure

- Insufficient surgical or colposcopic technique
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- Glandular involvement
- Grade of CIN
- Lesion diameter
- Status of surgical margins

**Subsequent Pregnancy Effect**

Cold-knife conization has been recognized to increases a risk of future preterm labor, a low birthweight infant, and cesarean section (14). It is demonstrated that all three methods of conisation (LEEP, electroknife and cold knife) increases the risk of preterm delivery (15).

**Summary**

Expectant management is recommended for CIN I, especially in adolescents and young women. Treatment of patients with CIN 2, 3 is recommended, due to low rate of spontaneous regression and high rate of progression. Ablative and excisional procedures have equally effective cure rates. LEEP is suggested as an office procedure with ease of use, providing a histologic specimen at low cost and morbidity, and high rate of success. Cold knife conization is recommended for women with suspected microinvasion, and suspected adenocarcinoma in situ.

**References**


