CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN)
ANATOMY OF CERVIX

• The cervix constitutes the lower third of the uterus.
• It is in two parts, the endocervix and the ectocervix.
• Ectocervix is covered with squamous epithelium.
• Endocervix is covered with columnar epithelium.
• **Squamocolumnar junction (SCJ)** - the meeting of two types of epithelium

• **Transformation zone** - that part of cervix, between originally and new SCJ.

• Transformation zone is the site where premalignant and malignancy develop.

• HPV infection can persist in the region of the TZ where metaplasia occurs.
Transformation zone showing position of abnormal cells

Diagram showing the transformation zone on the cervix
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CIN

Definition

• It is a premalignant lesion of cervix characterized by dysplasia and/or neoplastic changes which are confined to epithelium.
<table>
<thead>
<tr>
<th>WHO</th>
<th>Mild Dysplasia</th>
<th>Moderate Dysplasia</th>
<th>Severe Dysplasia</th>
<th>Carcinoma Insitu</th>
<th>Bethesda</th>
</tr>
</thead>
<tbody>
<tr>
<td>CINI</td>
<td>LSIL</td>
<td>HSIL</td>
<td>HSIL</td>
<td>HSIL</td>
<td></td>
</tr>
<tr>
<td>CIN2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIN3</td>
<td></td>
<td></td>
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</table>

*LSIL: low-grade squamous intraepithelial lesion
*HSIL: high-grade squamous intraepithelial lesion
CIN Cytology

Cytologic aberrations seen in CIN include:
- hyperchromaticity,
- abnormal chromatin distribution,
- Increased mitotic activity
- Large nuclei
- increased nuclear to cytoplasmic ratio and nuclear pleomorphism.

• These abnormalities may be seen in exfoliated cells in a Pap smear
CIN Histology

- CIN grading is based upon the proportion of the surface epithelium composed of undifferentiated cells characteristic of the basal layer.
- Increasing grade is associated with a progressive loss of epithelial maturation
Cervical Intraepithelial Neoplasia CIN

• CIN 1  = <1/3 thickness of epithelium

• CIN 2  = 1/3 – 2/3 thickness.

• CIN 3  = 2/3 – Full thickness
CIN

<table>
<thead>
<tr>
<th>Normal</th>
<th>CIN I</th>
<th>CIN II</th>
<th>CIN III &amp; CIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Mild Dysplasia</td>
<td>Mild Dysplasia</td>
<td>Moderate Dysplasia</td>
<td>Severe Dysplasia</td>
</tr>
</tbody>
</table>

Diagram showing the progression from normal to severe dysplasia and carcinoma in situ.
• CIN is a disease of continuum i.e. CIN 1 can progress to CIN 2, CIN 2 can progress to CIN 3, CIN 3 can progress to invasive carcinoma

• One third of CIN 3 cases develop into invasive carcinoma cervix over 20 years

• Some CIN persist or regress
# Natural History of CIN

<table>
<thead>
<tr>
<th></th>
<th>Regression %</th>
<th>Persist %</th>
<th>Regression %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN1</td>
<td>57</td>
<td>32</td>
<td>11</td>
</tr>
<tr>
<td>CIN2</td>
<td>43</td>
<td>35</td>
<td>22</td>
</tr>
<tr>
<td>CIN3</td>
<td>32</td>
<td>56</td>
<td>12</td>
</tr>
</tbody>
</table>
INCIDENCE

• Peak incidence - 25 and 29 year of age

EPIDEMIOLOGY AND AETIOLOGY

• Infection with the human papilloma virus (HPV)
• smoking
# Common HPV Types and their Effects

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>HPV Types</th>
<th>Leads to:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81</td>
<td>Benign cervical changes, Genital warts</td>
</tr>
<tr>
<td>High Risk</td>
<td>16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82</td>
<td>Precancer cervical changes, Cervical cancers, Anal and other cancers</td>
</tr>
</tbody>
</table>
• HPV 16 & 18 responsible for 70% of cervical cancer
• HPV 31, 33, 45 accounting for 12% of cervical cancer

• Persistent high risk infection (HR-HPV) can lead to cervical cancer in 10-15 years (minimum 7 years)

• Compared to the risk of uninfected women, risk of developing SCC of cervix is about 400 times higher following HPV 16 and 250 times higher following infection with HPV 18
Risk of HPV Infection

• Lifetime risk of infection up to 80% in exposed individuals.

• Peak incidence soon after the onset of sexual activity.

• Most infections usually clear within a few months, and about 90% clear within two years.
• Persistent infection occurs in 10-15% of women.
• Persistent high risk infection (HR-HPV) can lead to cervical cancer in 10-15 years (minimum 7 years).
• Compared to the risk of uninfected women, risk of developing SCC of cervix is about 400 times higher following HPV 16 and 250 times higher following infection with HPV 18.
Progression of cervical disease after HPV infection

* Probability increases with viral DNA integration. CIN: cervical intraepithelial neoplasia; ASCUS: atypical squamous cells of undetermined significance.

Smoking

• related to the immunosuppressive effects of nicotine derivatives within the cervix
• may act as a cofactor with HPV in triggering the development of CIN.
**Risk Factors for CIN**

- Early onset of sexual activity
- Multiple sexual partners (of self or of the partner)
- Low socioeconomic status
- Tobacco smoking (2 fold)
- Oral contraceptives more than 5 years (2.5 fold)
- Other STI like HSV, Chlamydia
- Immunosuppression such as, HIV (5 fold), use of immunosuppressive agents
- Natural history of HPV
Screening methods

1. Cytology
   A. conventional (Pap smear)
   B. liquid-based cytology (LBC)

2. Visual inspection
   A. acetic acid (VIA)
   B. Lugol’s iodine (VILI)

3. HPV DNA testing
4. Colposcopy
Papanicolaou Test (Pap smear)

• Cytological examination of a smear of cells taken from the cervix, specifically from the SCJ
• It is a screening test, not a diagnostic test.
• A pap test can also test for HPV (Human Papilloma Virus).
Papanicolaou smear test

• Results usually reported as:
  ➢ Normal
  ➢ Inflammation
  ➢ Atypical Cells of Uncertain Significance (ASCUS)
  ➢ LGSIL
  ➢ HGSIL
  ➢ Cancer
Time to collect Pap smear

• Mid-cycle, (day 10-20)
• a better sample if the patient is not bleeding and does not have an infection at the time of collection

• Patients should be told **not to:**
  • have sex, use a tampon or vaginal medication for the 24 hours prior to a pap test.
- Junction of pink cervical skin and red endocervical canal
- Inherently unstable
- Key portion of the cervix to sample
- Most likely site of dysplasia
- Concave end to fit the cervix
- Convex end for vaginal wall and vaginal pool scrapings
- Use concave end
- Rotate 360 degrees
- Don’t use too much force (bleeding, pain)
- Don’t use too little force (inadequate sample)
• Insert ~ 2 cm (until brush is fully inside canal)
• Rotate only 180 degrees (otherwise will cause bleeding)
Conventional cytology (schematic diag./pic)

Endo cervical brush placed inside endo-cervical canal

Tip of Ayre’s spatula placed at external os
- As thin as possible
- Properly labeled
- Within 10-15 seconds
- Allow to fully dry before packaging
- Cytologic Fixative (hairspray works acceptably also)
Diagnosis by Pap Smear

Mild Dyskaryosis

Moderate Dyskaryosis

Severe Dyskaryosis

Normal cell
**Liquid-based cytology _LBC**

- Liquid-based cytology allows Pap specimens to be collected into a liquid solution,
- machine processed into thin layer *(monolayer)* preparations on a glass slide.
- Liquid base cytology collects the whole sample from the sampling device in a liquid medium that is sent to a laboratory for processing.
- Affords a consistent identification of abnormal cells

- Thin Prep
- AutoCyte Prep
• LBC reduces the proportion of inadequate smears and it increases detection of true dyskaryosis.
• It is more expensive than conventional cytology.
• No evidence that LBC improves accuracy and detection of abnormalities.
Liquid Based Cytology (schematic diag./pic)

Brush for taking liquid based cytology & vial containing specimen transport medium

LBC brush placed at external os & rotated 3-5 times
Recommended target ages and frequency of cervical cancer screening (WHO)

✓ Recommended **target age 35-45 years**
✓ **3 year** screening interval for **25-49 years**
✓ **5 year** screening interval for **over 50s**
✓ Not necessary after 65 if last two smears are negative
✓ If a woman can be screened **only once** in her lifetime, the best age is between **35 and 45 yrs**
# UK NHS Cervical Screening Programme (2003)

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Frequency of screening</th>
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<tbody>
<tr>
<td>25</td>
<td>First invitation</td>
</tr>
<tr>
<td>25 - 49</td>
<td>3 yearly</td>
</tr>
<tr>
<td>50 - 64</td>
<td>5 yearly</td>
</tr>
<tr>
<td>65+</td>
<td>Only screen those who have not been screened since age 50 or have had recent abnormal tests</td>
</tr>
</tbody>
</table>
HPV DNA test

• Aims to detect the viral genome.
• Three potential clinical applications of HPV DNA testing
  • In primary screening; HPV testing with or without cytology - significantly more sensitive but also significantly less specific
  • Combination of HPV test and cytology allows earlier detection of high grade lesion. They can be used in conjunction with cytological or other screening tests, where sufficient resources exist. (a Pap result of “atypical cells of undetermined significance” (ASC-US))
• In the follow up after treatment; HPV testing with or without cytology has the potential to enhance the detection of treatment failures.

• HPV DNA-based screening should not begin before 30 years of age.
HPV DNA test (schematic diag.)

Collection of cervical cells

Brush for cervical cell collection & vial containing specimen transport medium
Colposcopy

• Colposcopy is the outpatient examination of the magnified cervix using a light source.
• It comprises lower-power magnification and illumination of the lower genital tract after applying various stains; acetic acid (3-5%) and Lugol’s iodine.
• It is used for both diagnosis and treatment.
Colposcopy

- Magnified Inspection of the Cervix
- Identifies the area of abnormality for biopsy & defines the extent of the cervical lesion
- Colposcopy is recommended only as a diagnostic tool and should be performed by properly trained and skilled providers.
Current indications for referral for colposcopy
• 3 consecutive inadequate smears
• 2 smears showing borderline nuclear changes in squamous cells
  2 smears showing mild dyskaryosis
  1 smear showing moderate or severe dyskaryosis
  1 smear showing possible invasion
• 1 smear showing borderline nuclear changes in endocervical cells
• 1 smear showing glandular neoplasia
• Any grade of dyskaryosis following treatment for CIN before return to routine recall
• 3 abnormal smears of any grade over a 10-year period
• Suspicious symptoms and abnormal cervix

• Smear with possible invasion or glandular neoplasia – should be seen urgently within 2 weeks of referral.
• Moderate or severe dyskaryosis – within 4 weeks
• Other abnormal results - within 8 weeks
Acetic acid test (with 5% acetic acid)

- Normal – no change
- Abnormal vascular pattern – Mosaicism (crazy paving appearance) or punctation.

Normal Cervix with Acetic Acid
lei. CIN – acetowhite area due to coagulation protein of cytoplasm and nucleic
**Schiller’s test** (with Lugol’s iodine)
- Normal – Mahogany brown
- CIN – no change
- Colposcopy directed biopsy from abnormal area
- Recent method of cervical screening is liquid based cytology
Diagnosis and Confirmation of CIN

By histological examination

• cervical biopsy (punch or excisional biopsy)
• Colposcopically directed biopsy
Treatment of CIN

The standard practice is

• to screen women using cytology (Pap test)
  ↓
  • when cytology results are positive
    ↓
    • diagnosis of CIN is based on biopsy of suspicious lesions
      ↓
      • treatment only when CIN2+ has been histologically confirmed
Alternative treatment approach

• An alternative approach in low resources areas, to diagnosing and treating CIN is to use a ‘screen-and-treat’ approach.

• The treatment decision is based on a screening test, and not on a histologically confirmed diagnosis of CIN2+.
Management of CIN lesion

• Counseling the patient about diagnosis, nature of diseases and treatment options.

For CIN 1,
- Intervention → ablation and excision.
- Conservative treatment as (CIN 1) may regress spontaneously in up to 60 per cent of cases
For CIN 2 and CIN 3,

1. Ablative technique
   - Not invasive, easy to perform, done with LA.
     No histology is available, not detect margin of clearance.

2. Excisional technique
   - Difficult to learn, longer to perform, done with GA, excellent histology, detect margin of clearance.

3. TAH
# Treatment of CIN

<table>
<thead>
<tr>
<th>Ablative Techniques</th>
<th>Excisional Techniques</th>
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<tr>
<td>Cryotherapy (Cryosurgery)</td>
<td>LEEP/LLETZ</td>
</tr>
<tr>
<td>Cold coagulation</td>
<td>Laser conization</td>
</tr>
<tr>
<td>Electrodiathermy</td>
<td>Cold knife conization</td>
</tr>
<tr>
<td>Laser ablation</td>
<td>Hysterectomy</td>
</tr>
</tbody>
</table>
• **Cure rates** for both – over 90%

• **Aim** of treatment - to remove the entire transformation zone

• **Choice** of techniques relies on the individual case, the colposcopic appearance, depth, severity and size of the lesion, type of the TZ, age, fertility and wishes of the woman, clinician’s experience and preference and equipment availability
Ablative methods

- destroy TZ
- accurate pre-treatment biopsy samples are needed
- All treatment techniques should remove tissue to a depth of > 7 mm to ensure eradication of CIN that may involve the gland crypt.
- Ablative methods are contraindicated in glandular lesions, suspicion of invasion and history of previous treatment
Cryotherapy

- Cryotherapy, where the cervix is frozen with liquid nitrogen as an outpatient.
- Not need anaesthesia
- It destroys tissue by freezing
- cheap and widely available.
- It is sufficient treatment for low-grade CIN, but not effective enough for high-grade disease.
Cryotherapy is the freezing of the abnormal areas of the cervix by the application of a very cold disc to them
Coagulation

- Uses temperature over 700C
- Painful
- Under GA
- It is a destructive treatment,
- Is effective for both high- and low-grade CIN
- But does provide a specimen.
- Easy

- Complications – Bleeding, sepsis, cervical stenosis
Cold coagulation apparatus with probes
Laser ablation

- Gives good control over depth of destruction
- Good haemostasis
- Excellent healing
- Particularly useful for treating lesions with vaginal involvement
- Disadvantage – not available to all units since the cost of equipment
Electrodiathermy

• Requires general, regional or local anaesthesia
• Possible to destroy up to 1 cm depth
• Cheap and easy to maintain
• May be considerable more thermal necrosis than anticipated
Excisional Method
Loop diathermy (large loop excision of transformation zone, LLETZ).

- (LLETZ = Large Loop Excision Of Transformation Zone)
- (LEEP = Loop Electrosurgical Excision Procedure)
- An excisional method, using a thin electric wire (electrosurgical unit) to remove the entire TZ and the affected tissue
- Under local anaesthesia
- The loop cut and coagulate at the same time
- 90% effective in treating women for precancerous lesions the first time used
- Roller ball can be used for haemostasis.
Large loop excision of transformation zone (LLETZ)
(LEEP)

The doctor will insert a speculum into your vagina in the same way as for a pelvic exam. The loop is inserted into the vagina to the cervix. Different sizes and shapes of loops can be used.

A close-up view of the surface of the cervix shows areas of abnormal cells.

The loop is used to cut away a thin layer of the cervix.

The loop removes the abnormal tissue from the cervix.
The **advantages** of this excisional technique

- clinically effective (95 per cent of patients have negative smears at six months),
- cost-effective (patient can be treated at the first hospital visit) and
- it provides a specimen for pathological assessment
- It is associated with relatively short duration
- It is of good compliance
- It is simple
Disadvantages of LEEP

• chance of severe bleeding
• Women may have a brown or black discharge for up to two weeks after LEEP
• Need training
• Best carried out in facilities where back-up is available for management of potential problems
Conization

- Excisional conization of the cervix can be performed either with a cold knife or with the carbon dioxide laser.
- Done under general anesthesia in the hospital by a gynecologist.
- Cone biopsy removes the entire circumference of the transformation zone and most of the cervical canal.
Cold knife conization

• Increased risk of haemorrhage, fertility and pregnancy morbidity

• Cone biopsy
  • Its disadvantage- risk of cervical stenosis or incompetence (5%).
  • Post treatment require close follow up with regular cervical smears 6 monthly after treatment and then yearly for ten
Micromanipulator used to control laser beam using colposcopic guidance

Control for focusing laser and varying spot size 0.2–2 mm

CO2 laser controls which can vary the power of the laser beam
Cone biopsy

Cold cone biopsy: a large area of tissue around the cervix is excised for examination.

Cervix viewed through speculum with patient in lithotomy position.
COLD KNIFE CONIZATION

Surgical removal of a cone-shaped area of the cervix
COMPLICATIONS OF CIN TREATMENT

Early
- Peri-operative pain
- Primary haemorrhage (<1%)
- Secondary haemorrhage (within 2 weeks from treatment and is usually related to infection)

Late
- Cervical stenosis
- Cervical incompetence, risk of preterm delivery and LBW by cold knife cone biopsy, laser conization and LLETZ
  - Increased risk of PROM by LLETZ, Laser ablation
Follow up after treatment of CIN

• Women who have undergone treatment remain at risk of recurrent/residual disease
• Risk of developing future invasive cancer is also 4-5 times greater than general population
• Need close cytological and colposcopic follow up following treatment
• Women after **hysterectomy** for CIN require a repeat smear at 6 and 18 months and no further surveillance
• If there is uncertainty of excision, screening should continue as if the cervix was still in situ.
Glandular disease

• Incidence of glandular disease is increasing (CGIN)
• A higher incidence now recorded in women under 35.
• 20-35% of cervical tumours – adenocarcinoma or adenosquamous carcinoma
• More aggressive course than squamous counterparts
• Poorer prognosis that partly might reflect delay in diagnosis.
• HPV 18 – associated with glandular lesion
• Atypical glandular cytology – suggest possibility of invasive cervical adenocarcinoma or CGIN
• If endometrial cells are seen on cytology report in post-menopausal woman not taking HRT indicate endometrial disease and should be investigated appropriately.
• If borderline glandular changes are present → colposcopic assessment with appropriate cervical biopsies and selective endometrial biopsy are indicated.

• **Punch** biopsy in atypical glandular cytology is unreliable, as the lesions are often small and may occur in the base of gland crypts, **excisional** biopsy is recommended.

• Majority (90%) – located within 1 cm from SCJ and co-exist with CIN, although they can be found potentially anywhere in the endocervical canal.
• CGIN – excisional treatment and adequate follow-up
• Margins – should be disease free
• If margins involved – further excision treatment may be undertaken
• Option of hysterectomy should be considered in after completion of childbearing
Hysterectomy

Still retains a place in the management of CIN in women who have other gynaecological conditions such as fibroid, menorrhagia or prolapse.

May also be used in glandular lesion where fertility does not need to be spared, especially in cases of treatment failure or incomplete excision.
THANKS