FGS - fair Notes

① Carcinoma cervix.

HINTS

- Post coital bleeding.
- Small growth - friable on PV that bleeds on touch.
- Foul smelling - white discharge
  "No Babe, Not candida"
- Ulcero proliferative growth in cervix, anterior lip of cervix ... whatever.

" Its a bit confusing I know...
especially with white discharge!!

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① provisional diagnosis?
② etiopathogenesis and morphology of lesion: - gross & MC.
③ How do you establish the diagnosis?
④ staging of the condition
⑤ preventive strategy
⑥ Screening method
⑦ prognosis of lesion
⑧ How could it be early detected?
⑨ Microscopic types?
⑩ Cervical Intraepithelial Neoplasia (CIN).

Etiopathogenesis

not HPV alone.
HPV + Synergistic factors

Causative agent

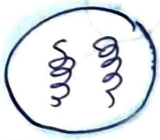
High risk - HPV - types 16, 18 (MC)
31, 33 (less common)

they are sexually transmitted and are associated with Cancers of Cervix, Anogenital region & oropharynx. {eg: tonsillar mucosa}

Low risk (6, 11) → condyloma accuminatum.

High risk (16, 18) → high oncogenic potential.
↓
Cervical Carcinoma.

Pathogenesis



Benign lesions → HPV genome remains episomal.

Malignant lesions → HPV genome gets integrated into host DNA.

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persistent HPV infections require viral entry into immature Basal epithelial cells.

Site most vulnerable - squamo columnar junction or transitional zone of cervix

High-risk HPVs 16, 18

↓

HPV genome is integrated into host DNA, not episomal.

↓

Integration site: Random, but clonal.

↓

Disrupts E_1/E_2 region, causing.

↙ ↘

loss of E_2, a viral repressor

Overexpression of oncoproteins E_6 & E_7

HPV → (• HPV exposure • Sexual activity • Immune status • other factors) → High risk HPV 16, 18 → LSIL → HSIL → Invasive carcinoma → metastasis.

Extra info:

- P53 polymorphism at codon 72:
  - Arg 72 variant → more prone to E_6 degradation.
  - ↑ risk of Ca in people having Arg 72 P53 polymorphism

Action of HPV oncoproteins

E_6 → TERT (upregulation) → increased telomerase expression.

E_6 → P53 → Binds & degrades P53

E_7 → P21 → Inhibition of P21, P27 (CDK inhibitors)

↑ CDK4 / cyclin D

E_7 → RB-E2F → Inhibition of RB.

⊖ of RB&E2F

free E_2F → promotes $G_1 \rightarrow S$ phase progression.

Result:
- Immortalization
- Increased cell proliferation..
- Genomic instability.

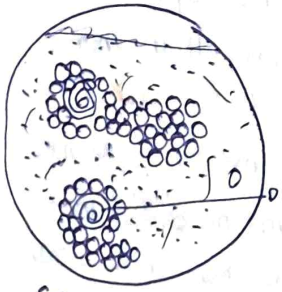
Synergistic factors in Carcinogenesis:

- HPV infection ≠ sufficient for malignancy.
  - alone → not
  - cause → in vitro HPV immortalized keratinocytes don't form tumours unless co transfected by with mutant RAS.

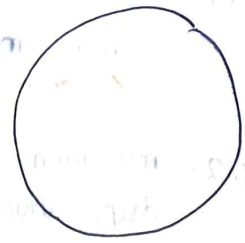
Co factors required

- Genetic : RAS mutation.
- Environmental – Smoking ✓
  Co infection (HIV) ✓
  Hormonal factor ✓
  nutritional deficiency.
- Immunologic – weak immunity ✓
  ↓
  persistant infection ✓
  ↓
  higher risk. ✓

* HIV coinfection – significantly ↑ risk. ✓



SCC - Keratinizing.



early stromal invasion.

MORPHOLOGY

GROSS

Two main growth patterns:

① Fungating (Exophytic) : outward, cauliflower like mass.

② Infiltrative : deply invades cervical stroma as a hard, irregular mass

Histological Types

① Squamous cell carcinoma (75%)

MICROSCOPY

- Nests and tongues of malignant squamous epithelium.
- Maybe Keratinizing or non-Keratinizing.
- Invasion ~~which~~ with of underlying cervical stroma.

② Adenocarcinoma (15%)

- arises from endocervical glandular epithelium.

MICROSCOPY

- Malignant glandular structures.
- composed of malignant

malignant endocervical cells with

- large, hyperchromatic nuclei and relatively mucin depleted cytoplasm.

↓ ↓ ↓

- results in dark appearance of the glands, compared to normal endocervical epithelium.

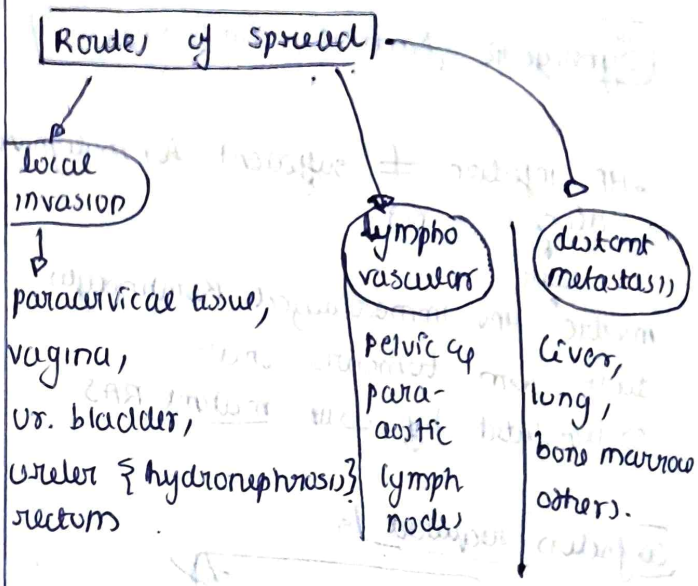
3. Adenosquamous Carcinoma

- composed of intermixed malignant squamous & glandular elements.
- aggressive tumour.

4. Neuroendocrine carcinoma.

Microscopy

- resembles small cell carcinoma of lung.
- but differs in being positive for high risk HPV's.
- highly aggressive tumour.



STAGING

Stage 0 – Carcinoma in situ (CIN III, HSIL)

Stage I – Ca. confined to cervix.

- Ia – preclinical carcinoma, that is, diagnosed only by microscopy.

Ia1 – stromal invasion no deeper than 3mm and no wider than 7mm.
≤ 3mm depth, ≤ 7mm width

Ia2 – maximum depth of invasion of stroma deeper than 3mm and no deeper than 5mm, and no more than 7mm width.
>3mm, ≤5mm d ≯ ≤ 7mm width.

Ib – histologically invasive carcinoma. confined to cervix and greater than Stage Ia2

Stage II – carcinoma extends beyond the cervix but not to the pelvic wall.

- carcinoma involves the vagina but not the lower third.

Stage III – Carcinoma has extended to pelvic wall.
on rectal examination, there is no cancer-free space btw tumour and pelvic wall.

- tumour involves lower 1/3 of vagina.

Stage-IV – carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum.

- also includes cancers with metastatic dissemination.

Preventive strategy

1. Primary prevention.

HPV vaccination.

- most effective preventive measure against cervical cancer.

- recommended for.
  - Girls & boys aged - 11-12 years.
  - young men & women upto 26 years of age.

2 FDA approved vaccines.

Cervarix (Bivalen)	HPV 16, 18	female 9-25 years.
Gardasil	HPV 6, 11 16, 18	male & female 9-26 years.

2. Secondary Prevention. – Screening.

- detects precancerous lesions (LSIL / HSIL) before invasion.

→ cytological pap smear

→ HPV – DNA testing

→ colposcopy for abnormal results.

3. Other preventive Measures

- Health education & awareness
- promotion of safe sex practices.
- Smoking cessation.

SCREENING METHOD

figure

1. cytologic Screening by pap smear examination.

✓ cytological screening has significantly ↓ mortality from cervical cancer.

pap smear – cytological screening test that detects abnormal exfoliated cells from the transformation zone.

method: Spatula/Brush used to collect cells
↓
transformation zone of cervix is circumferentially scraped and cells are smeared onto slide
↓
fixed & stained (papanicolaou stain)
↓
cytological evaluation

Spatula/Brush
↓
transformational zone of cervix is circumferentially scraped with Ayre's spatula/Brush

- **Conventional**
  - ↓
  - cells are smeared onto a slide
  - ↓
  - fixation – 95% ethanol
  - ↓
  - Pap staining (HOPE)
  - ↓
  - cytological evaluation
  - ↓
  - reporting: Bathesda system - adequacy
- **liquid Based cytology**
  - ↓
  - Brush put into container having alcohol
  - ↓
  - Sure path/thin prep (2 devices)
  - ↓
  - cytological evaluation

② HPV DNA Testing.

- Molecular method detecting high-risk HPV types (16, 18 esp).
- higher sensitivity but lower specificity
- Indication: woman ≥ 30y (as cotest with Pap)

- not recommended in < 30 years of age.

due to - ↑ incidence of infection.
- low specificity of test during that period.

3. Follow-up of Abnormal cytology.

- colposcopy

- visual exam of cervix / vagina under magnification after applying acetic acid.
- abnormal epithelium appear as

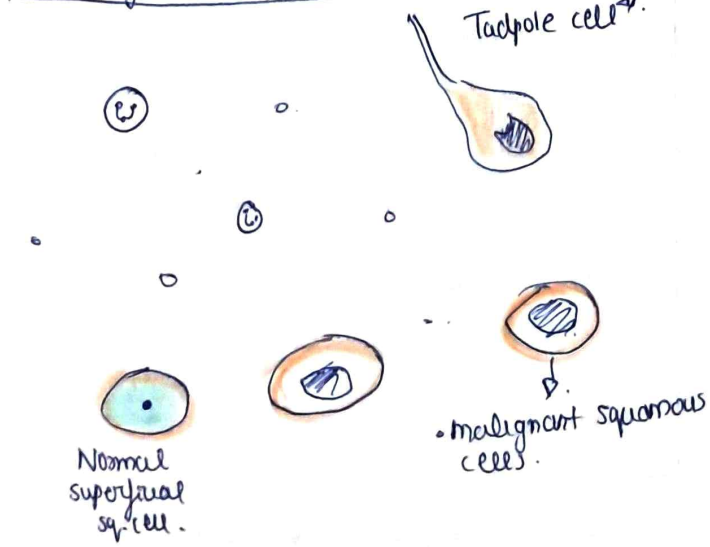
Aceto-white areas

- Targeted biopsy of suspicious areas:

LSIL : usually followed conservatively or ablated (cryotherapy)

HSIL : treated with cervical conization {superficial excision}

Cytological appearance of S.cc of cervix.



Screening Schedule.

- start at 21 years or within 3 years of onset of sexual activity.
- every 3 years till age 30
- after 30 years:
  - if PAP normal & HPV negative → screen every 5 years
  - if HPV (+) PAP normal → repeat PAP in 6-12 months
  - if PAP ab(N) → VIA.

age	
< 21 y	No testing needed.
21-30 y	PAP test every 3 years.
30-65	PAP test every 3 y PAP & HPV every 5 years.
> 65	No needed.

if abnormal PAP → colposcopic exam of cervix & vagina. by VIA visual inspection with acetic acid.

mucosa examined with magnifying glass after applying 5% acetoacetic acid, which highlights ab(N) epithelium as white spots (aceto-white areas)

Diagnosis establishment

① Colposcopic examination

- done after abnormal PAP smear or suspicious lesion on visual inspection.
- magnified visual inspection after application of 5% acetoacetic acid.
- acetic acid highlights abnormal epithelium as white areas.

"aceto-white changes"

due to increased nuclear density.

↓

these suspicious area are targeted for Biopsy.

② Biopsy of the Lesion.

- Targeted Biopsy taken from acetowhite areas.

↓ sent for

Histopathological Examination.

③ Histopathological Examination

Gold standard

⇒ Definitive step in establishing the diagnosis of invasive cervical carcinoma

Confirms:

- type {SCC, AC, NE etc}
- invasion extent
- depth & pattern of invasion.
- ~~Prognosis & lymphovascular invasion.~~

if you want... write Histological feature M/C of SCC, adeno etc.

CIN

draw figure FIRST.

- Cervical Intraepithelial Neoplasia.
- AKA Squamous Intraepithelial lesions (SIL).

presently used: Bethesda system SIL.

- CIN : refers to preconcerous epithelial changes in cervix caused by high risk HPV.

- It represents a non-invasive dysplasia confined to the squamous epithelium.

according to Bathesda reporting.

CIN classification ✓ (current WHO (two-tier))

- CIN I - mild dysp — LSIL
- CIN II - moderate — HSIL
- CIN III - severe. — HSIL

{reflects two-tiered management approach : conservative vs excisional}.

Association with HPV

- > 80% LSIL & ~100% HSIL are associated with high risk HPV.
- LSIL → productive infection with high viral replication.
- HSIL → deregulated viral gene expression (E6, E7), low viral replication, & proliferation.

LSIL (CIN I)

- Koilocytic atypia → irregular nuclear borders, nuclear enlargement, hyperchromasia, perinuclear halo.

- LSIL does not progress directly to invasive carcinoma & most cases regress spontaneously.

- only small % progress to HSIL.

- LSIL → productive HPV infection. high level of viral replication.
- atypical cells confined to lower 1/3 of epithelium.

HSIL (CIN II, III)

- HSIL is considered to be at high risk for progression to carcinoma.
- there is progressive deregulation of cell cycle by HPV, which results in increased cellular proliferation, arrested epithelial maturation lower rate of viral replication.
- Expansion of Basal cells into upper 2/3 or full thickness.

- loss of maturation, nuclear atypia throughout.

(1) ⇒ increased Ki-67 ✓

(2) ⇒ overexpression of P16.
due to (E7-mediated) disruption.

breast with
HSIL → cervical conization (excision)

Morphology

SIL – atypical immature squamous cells.

① Nuclear atypia : Nuclear enlargement.
pleomorphic nuclei
hyperchromasia.

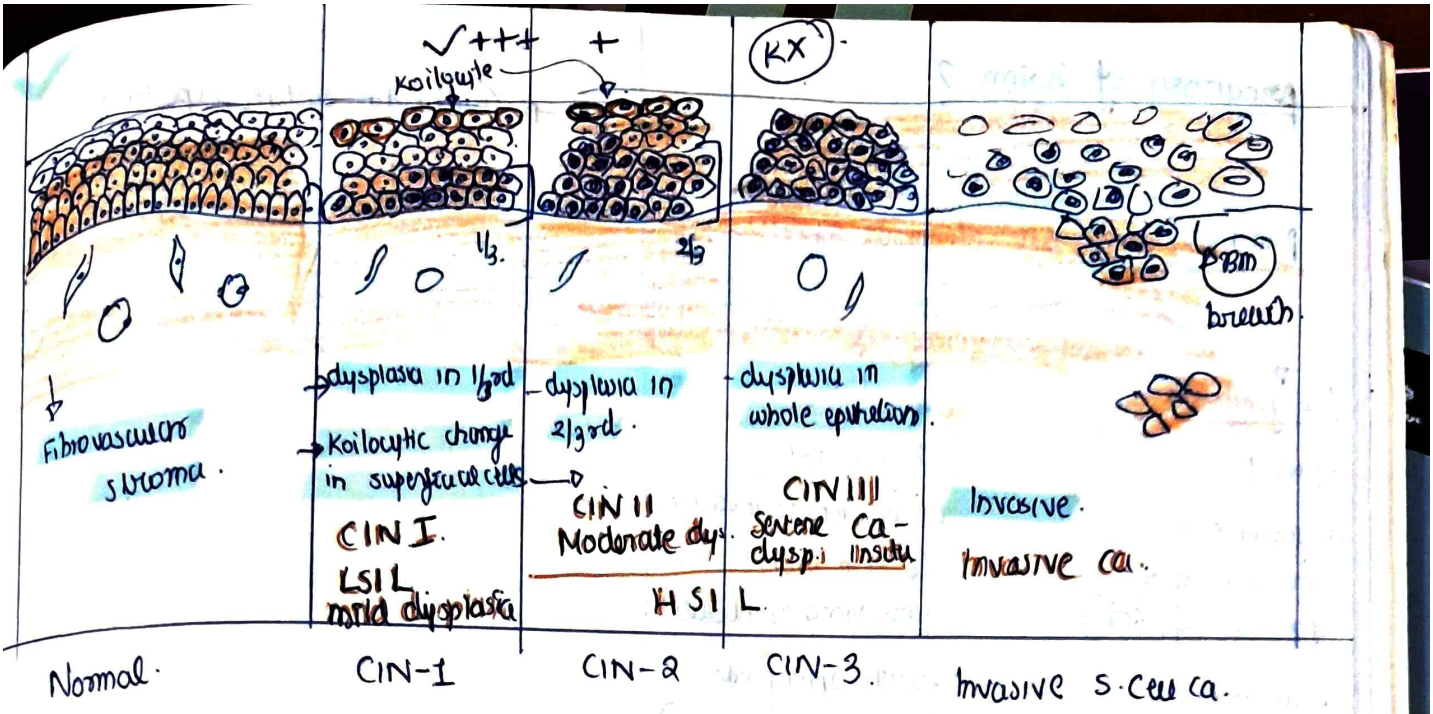
② ↑ N:C ratio

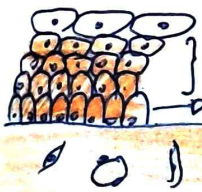
③ loss of polarity.

Koilocytic change. → (cytopathic effect of viral replication)

- in superficial cells mainly.
- raisinoid nucleus – enlarged ✓
wrinkled.
rop-like chromatin. ✓
- perinuclear halo
- peripheral dense cytoplasm.

→ Koilocytes are absent in many high grade dysplasia & all Invasive Ca.





Superficial – glycogen ✓, mature, not pink.
Intermediate – polygonal cells
Basal – columnar

Normal.

- HPV infects – immature sq. cells (Basal).
- replication of HPV – superficial layer. Koilocytic change.
- CIN 1 – active replication.

Koilocyte.

- perinuclear condensation of ectoplasm
- nuclear atypia : Bigger size, irregular boundary, hyperchromatic.
  - raisanoid
- perinuclear halo.

dysplastic cells.

prognosis of lesion ?

prognosis of SIL Bathesda system

low grade SIL

- good P
- majority are transient & regress spontaneously. (60%).
- low risk of progression to HSIL (10%)

CIN I

HSIL.

- higher risk of progression to invasive Ca, esp with persistance & untreated
- with appropriate treatment, (conization) excellent prognosis.

CIN II, III.

Invasive Ca.

prognosis depends on :

① stage at diagnosis. (most impt).

② tumour size, depth of invasion.

③ lymph node inv → worsens.

Survival rates

Stage I - 90-95% 5-year survival.

II - ~60-80%.

III - ~30-50%

IV < 20%

Other factors.

- Histological type - SSC - better prog.

  adeno, neuro] poor.