Review of normal anatomy and histology

The endocervix is lined by mucus secreting simple columnar epithelium with glands dipping down into the stroma. The ectocervix is lined by non-keratinizing stratified squamous epithelium. The squamo-columnar junction near the cervical os is where they meet. During the reproductive years, under the influence of oestrogens, the columnar endocervical epithelium near the os protrudes out onto the ectocervix where it is exposed to the more hostile vaginal environment and it undergoes metaplasia to stratified squamous epithelium (a normal process). The region at the cervical os that includes the squamo-columnar junction and metaplastic squamous epithelium is known as the transformation zone.

Acute and chronic cervicitis

A certain degree of cervical inflammation is common in most women. Specific (sexually transmitted) infections may also occur and are important due to their relationship with pelvic inflammatory disease. Inflammation may cause reactive cytological changes in epithelial cells causing abnormal cervical smear results.

Endocervical polyps


Cervical Carcinoma

- Common worldwide, particularly in developing countries
- Incidence has decreased in developed countries, including Australia, largely as a result of cervical screening programs, however, changes in sexual behaviour may have contributed
- Predisposing factors and pathogenesis:
  - Over 99.7% of squamous cervical carcinomas are found to contain Human Papillomavirus (HPV) DNA. Infection with HPV is necessary, though not sufficient, for development of cervical carcinoma
  - Other factors that may influence development include the hosts immune status (suppression of cell mediated immunity, including AIDS) and genetic makeup, cigarette smoking, use of oral contraceptive pill (OCP)
  - Develops from premalignant lesions caused by HPV (see later)
- Squamous cell carcinoma
  - Commonest type, > 80% of cancers of cervix
  - Peak incidence now 35-50 years of age for invasive cancer (in unscreened populations), depending on country, and 20-30 years of age for HSIL
  - Symptoms: may be asymptomatic, otherwise irregular vaginal bleeding, vaginal discharge, bleeding or pain on coitus, dysuria
  - Morphology
    - Often fungating mass, may be ulcerative or infiltrative lesion
    - Squamous differentiation histologically, various subtypes
  - Natural history
    - Spreads locally to uterus, vagina, bladder, ureters, rectum, peritoneum. May lead to ureteric obstruction and renal failure, infection
    - Lymphatic spread to pelvic nodes
    - Distant metastases
    - Treatment: hysterectomy and lymph node dissection, radiotherapy
  - Prognosis depends on stage, histologic type and grade.
- Adenocarcinoma
  - Also frequently associated with HPV
  - May be associated with dysplasia of the glandular epithelium
- Several other rare histological types
Human Papilloma Virus (HPV)
• Double stranded DNA viruses
• More than 100 types (genotypes) responsible for various lesions of squamous epithelium, mainly of skin and mucosa (e.g. genital)

Genital HPV and pathogenesis of cervical squamous carcinoma
• Low and high risk types for progression to cancer
• HPV6 and HPV11 responsible for genital and perianal warts (condyloma acuminatum), classified as low risk
• High-risk types include HPV16, 18, 45 and 31. Each has a different potential for oncogenic transformation. HPV16 is responsible for more than 50% of cancers in all studies.
• Infection with high-risk genital HPV is sexually transmitted. Probability of transmission is high, estimated to be greater than 50% following unprotected sexual intercourse
• Predisposing factors for infection: sexual history especially young age of first intercourse, multiple sexual partners, male partner who’s had multiple partners
• Prevalence of infection among sexually active young women is around 20% - 25%.
• Nearly half of sexually active teenagers will develop infection over a three-year period
• Infection may be with one or more HPV subtypes and these may change over time.
• Virus infects the host’s basal squamous cells, particularly the metaplastic squamous cells at the cervical transformation zone. Viral DNA is present within the host cell nucleus in episomal form. As the cells mature and differentiate, the viral genome replicates and new virions are made. Viral protein products lead to the characteristic changes of HPV infected cells (koilocytes) seen in the upper layers of the epithelium. Normal desquamation of mature squamous epithelial cells results in the release of virus particles
• Low grade lesions (CIN1/LSIL) result from viral replication and are considered to represent acute or productive viral infection. They are seen histologically by the presence of koilocytes and mild cytological abnormalities in the lower third of the squamous epithelium (CIN 1). These changes are referred to cytologically as a low grade squamous intraepithelial lesion (LSIL). Most LSIL/CIN1 regress spontaneously and are not generally treated as a premalignant lesion.
• In a small percent of these cases, the viral DNA is integrated into the host genome and high grade squamous intraepithelial lesions (HSIL) result. These are characterised by more severe degrees of atypia that extend into the mid–upper epithelium histologically (CIN 2 and 3). Dysregulation of the cell cycle is believed to result from the interference by viral proteins E6 and E7 in the function, or resulting in the degradation, of tumour suppressor proteins p53 and RB, pro-apoptotic proteins and by activating telomerase
• The majority of HPV infection (and related morphological changes) resolves spontaneously, estimates of the time frame range from 8 to 14 months. Persistent infection with high risk types carries a significant risk of progression to HSIL, however, even with high risk HPV types and high grade lesions, infection resolves spontaneously in a high proportion (possibly at least 80%) of women and leads to cancer in < 2% of cases.
• Data suggest that progression of low grade to high grade lesions and cancer is generally slow, usually taking many years, but can potentially progress more rapidly
• These lesions are asymptomatic and usually not visible to the naked eye
• HPV does not invariably give rise to cytological abnormalities and acute infection may sometimes give rise to high grade changes.
• HPV may also infect glandular and neuroendocrine cells of the cervix resulting in adenocarcinomas and neuroendocrine carcinomas respectively.
• HPV also causes approximately 35-50% of vulval and vaginal cancers

Histological and cytological changes of HPV and related lesions

Histological
• Changes seen in squamous epithelial cells
  • Cytological: nuclear enlargement and increase in N:C ratio, nuclear hyperchromasia, pleomorphism, excessive cell proliferation
  • Architectural: disorganisation and abnormalities in maturation
  • Koilocytes
• Grades of severity:
  • Mild (CIN 1): cytological atypia and disorganisation confined to lower third of epithelium
  • Moderate (CIN 2): cytological atypia and disorganisation confined to lower two thirds of epithelium
  • Severe (CIN 3) or carcinoma in situ: cytological atypia and disorganisation throughout full thickness of epithelium
• Changes are a continuum but grades give an estimation of the level of risk for developing invasive cancer if left untreated

Cytological
• Changes seen in squamous epithelial cells
  • Nuclear enlargement and increase in N:C ratio, nuclear hyperchromasia, pleomorphism
  • Koilocytes
• Grades of severity
  • Low grade squamous intraepithelial lesion (LSIL): refers to changes of koilocytosis and/or mild atypia seen in a cervical smear. Correlated to productive or acute infection of the cervix with HPV. Correlates to koilocytic change and/or CIN 1 on a cervical biopsy (histology).
  • High grade squamous intraepithelial lesion (HSIL): correlates to CIN 2 and/or CIN 3 on a cervical biopsy (histology). Cells with large atypical nuclei and high N:C ratio

Cervical screening
• Cervical screening programs have enabled detection and treatment of precancerous (dysplastic) lesions before they become invasive and earlier detection and treatment of invasive cancers with improved survival.
• Cervical screening initially became available for Australian women in the mid-1960s with a more organised national approach introduced in 1991 (National Cervical Screening Program (NCSP))
• The screening program involves general practitioners, gynaecologists, gynaecological oncologists, cytologists, pathologists, women's health nurses, and national and state governments
• The program has a number of components including improving communication and education for women, establishing a systematic approach to screening, reporting and management, encouraging the regular participation of women in screening programs, ensuring quality control in the reporting of cervical cytology and instituting approaches to the follow-up and management of screen-detected abnormalities.
• Utilises a cytological screening test, does not make a definite diagnosis and false negatives and positives (i.e. incorrect results) can occur. As such, histological confirmation of high-grade disease is advised before proceeding to treatment.
• Smear procedure: cells from the transformation zone of the cervix are sampled, applied onto a slide, fixed and sent to a pathology laboratory. Cells may be sampled with a spatula or brush and applied directly to a slide or placed in fluid for preparation of a ‘thin prep’ specimen. Cells are stained (Papanicolou or ‘Pap’ stain) and examined and reported.
• Subsequent patient management depends on the abnormality. In Australia, if no abnormalities, women are resmeared every 2 years. Patients with non-specific and mild abnormalities and HPV changes (e.g. LSIL) may just be screened more often so that if significant atypia develops it can be investigated quickly. Patients with more significant abnormalities including high grade dysplasias (HSIL) are referred to a gynaecologist for colposcopy (visualization of area) and targeted biopsy for more accurate histopathological assessment and subsequent treatment if necessary. There are National Guidelines as to the reporting of cervical smears and as to how the different abnormalities are followed up/managed.
• Cervical screening registries: keep records of smear and biopsy results plus send reminders to women when they are due for their next smear or gynaecologists appointment.

Prevention
Safe sex.
Gardasil
• A vaccine that helps protect against cervical cancer, precancerous cervical, vaginal and vulvar lesions and genital warts caused by the HPV types in the vaccine (6, 11, 16, and 18)
• To protect against acquiring infection, will not protect against HPV types to which the patient has already been exposed
• Vaccination will not substitute for routine cervical cancer screening
• The vaccine contains viral proteins made from recombinant technology

Further information can be found in the document: Screening to Prevent Cervical Cancer: Guidelines for the Management of Asymptomatic Women with Screen Detected Abnormalities. These guidelines can be downloaded from the NHMRC website: