PREMALIGNANT DISEASE OF THE CERVIX

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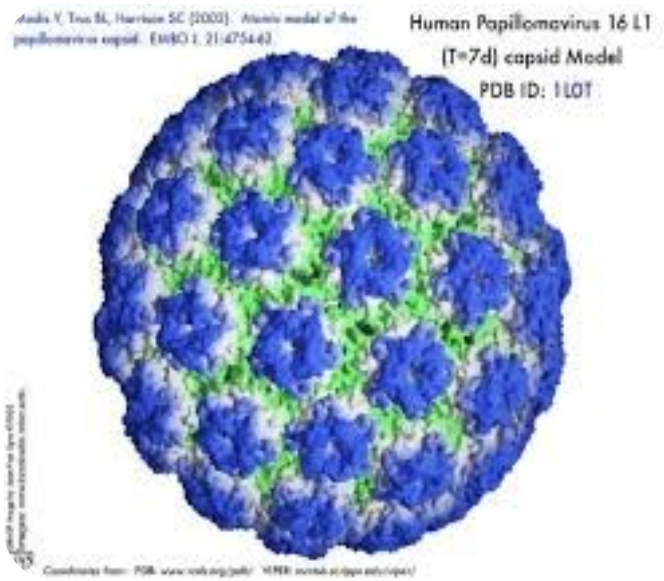
Epidemiology and etiology

- Cervical cancer is caused by persistent high-risk HPV infection. HPV is a small, double-stranded deoxyribonucleic acid (DNA) virus of which there are more than 100 different types. These are classified as low-risk or high-risk types, depending on their ability to cause cancer. Low-risk types HPV 6 and 11 cause benign warts, while high-risk types HPV 16, 18, 31, 33 and 45 cause cervical cancer.



HPV infection is spread during sexual intercourse. Infection is very common following the onset of sexual activity and up to 80% of adults show serological evidence of previous infection. Infection is usually transient and of no clinical consequence, but a minority of individuals develop a persistent genital infection that predisposes them to premalignant and malignant change

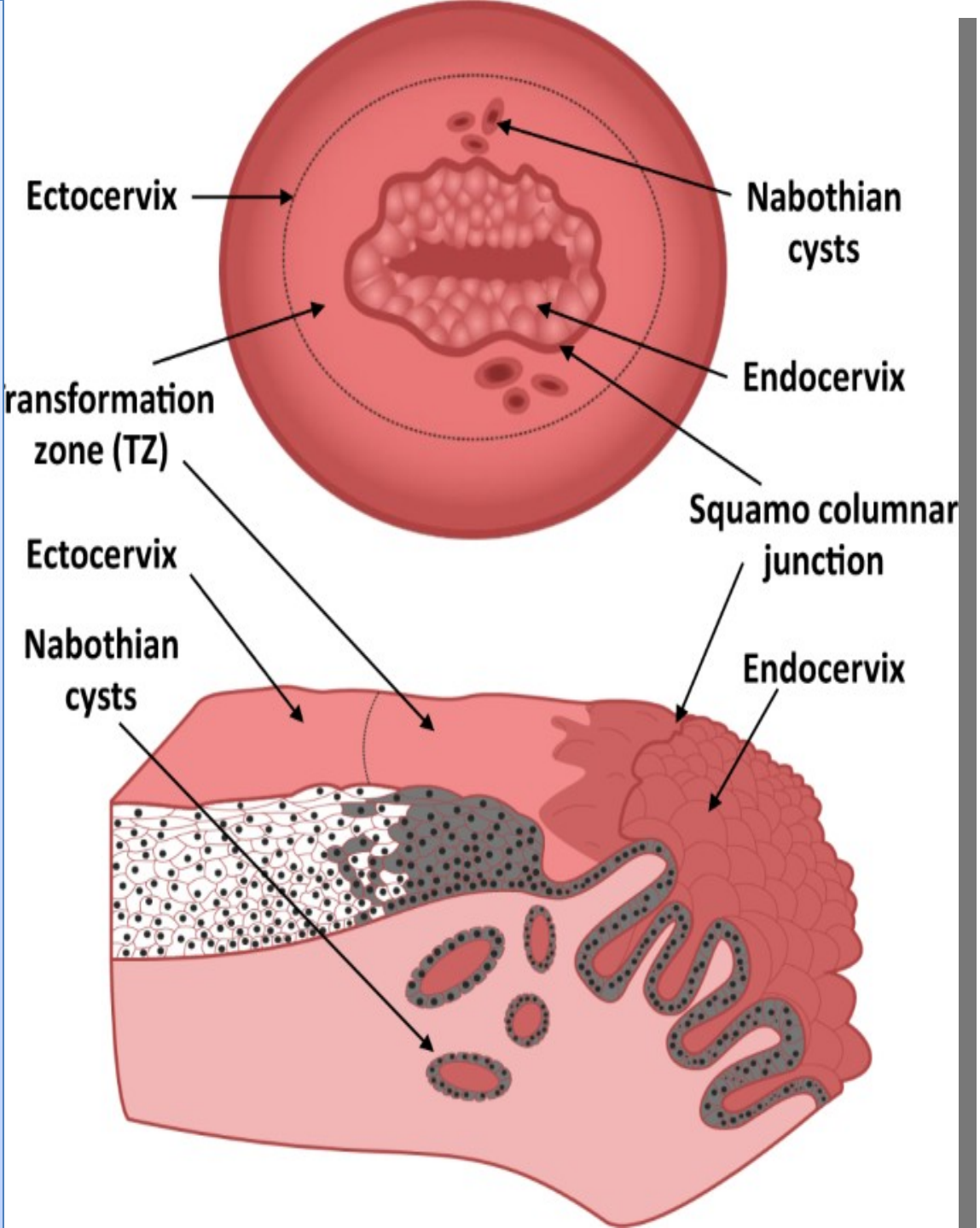
Smoking reduces the efficiency with which the virus is cleared by the immune system and increases the risk of persistent infection.

Women who are immunocompromised, for example those with human immunodeficiency virus (HIV) and transplant recipients on long-term immunosuppressive therapy, are particularly at risk of premalignant and malignant disease of the cervix

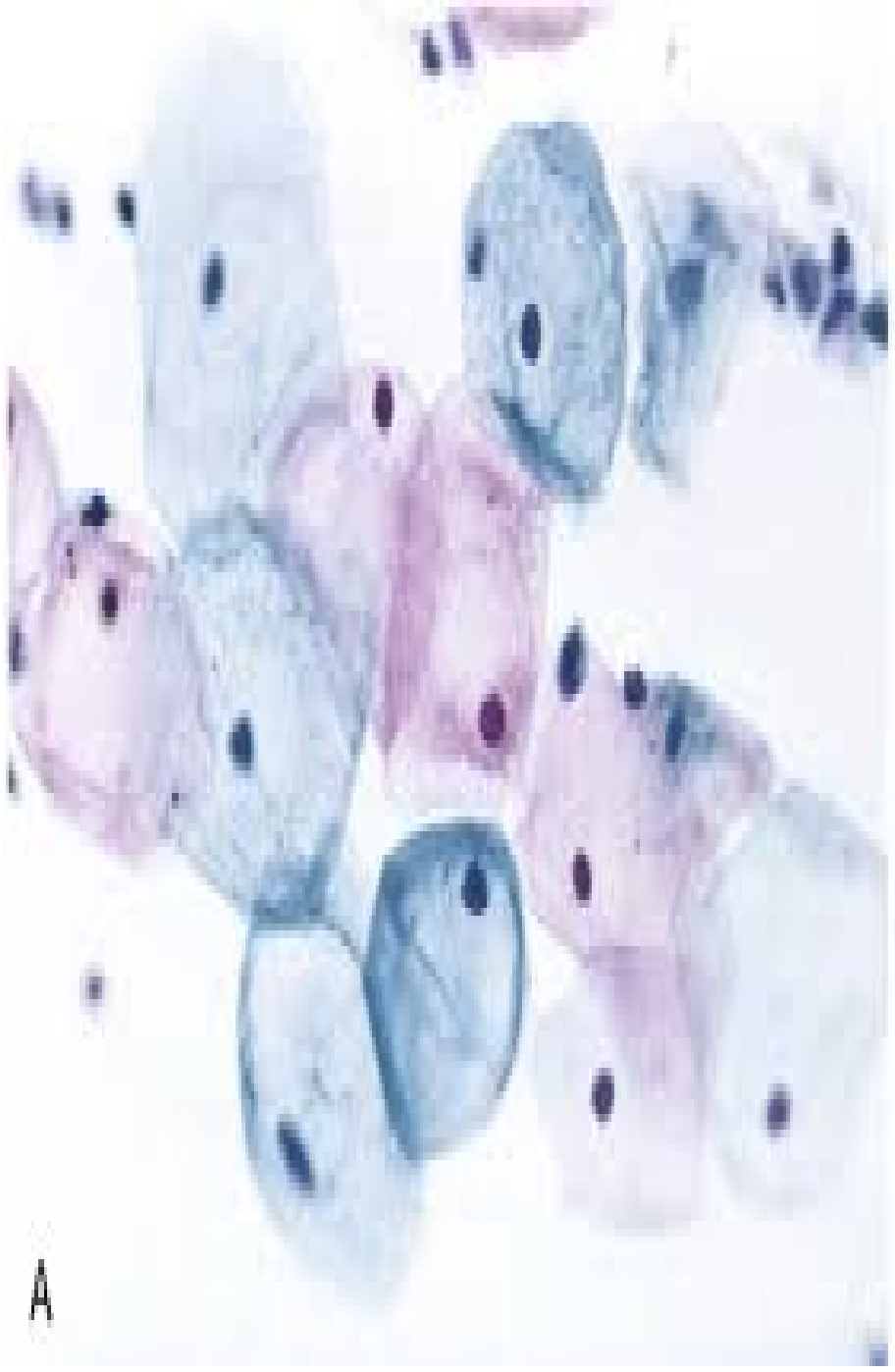
Pathophysiology

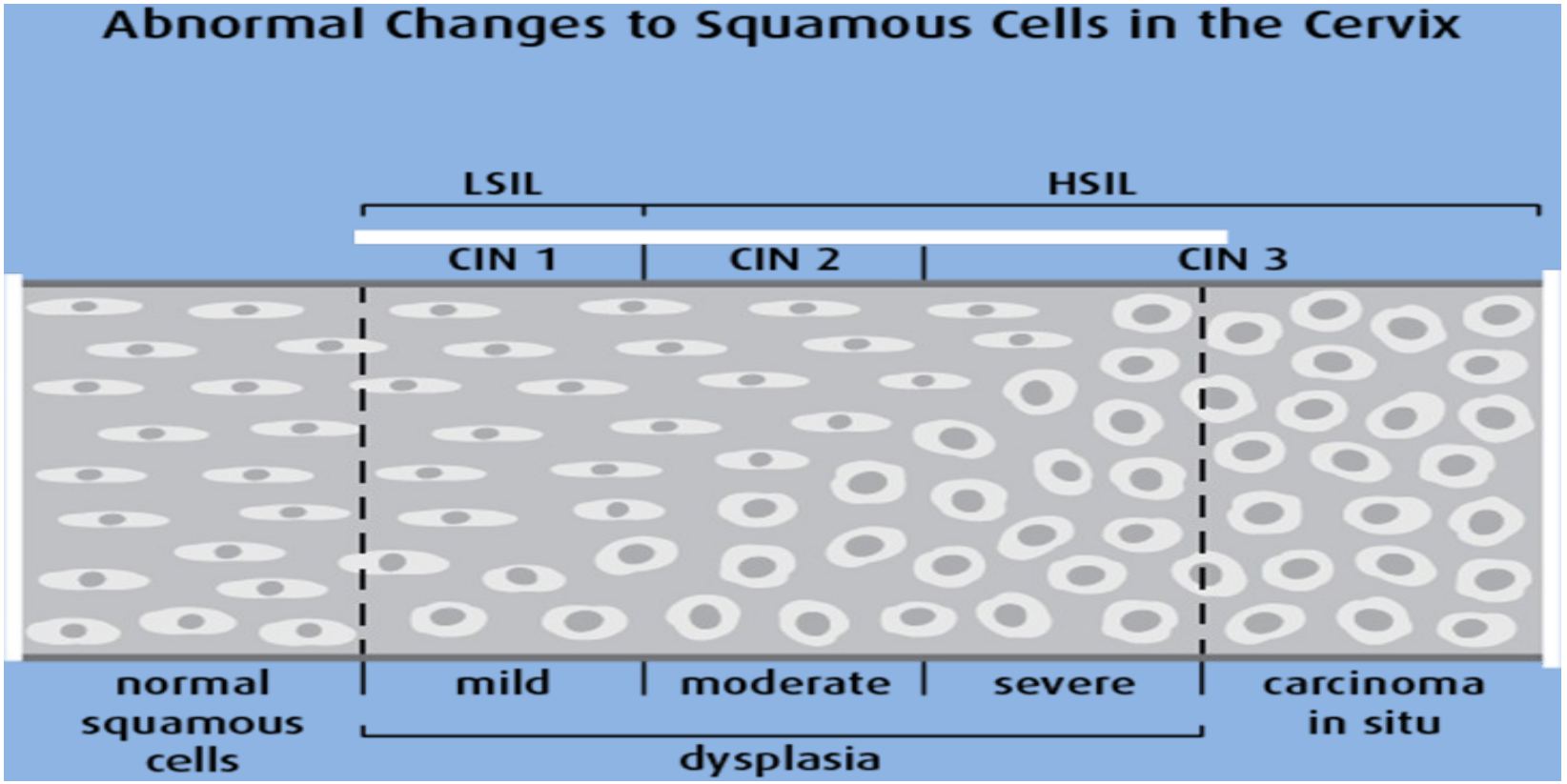
The tubular cervix is composed of stromal tissue covered by squamous epithelium in the vagina (ectocervix) and columnar epithelium within the cervical canal (endocervix). The endocervix contains many deep folds, called crypts, that are lined by columnar epithelium. The meeting of the two types of epithelium is called the squamocolumnar junction (SCJ) and this is usually on the ectocervix The position of the SCJ varies throughout life. In children it lies at the external cervical os, at puberty it extends outwards onto the ectocervix as the cervix enlarges, and in adult life it returns to the external cervical os through the process of metaplasia, which is the physiological transformation of columnar epithelium to squamous epithelium.

The so-called ‘transformation zone’ (TZ) is defined as the area between the original SCJ and the current SCJ where the epithelium changes from columnar to squamous epithelium over time. Sometimes the columnar epithelium is covered by squamous epithelium, leading to retention of mucus – this is called a nabothian follicle The TZ is the site where premalignancy and malignancy develop.



- When HPV infection persists in certain individuals, it triggers an oncogenic process in the region of the TZ where metaplasia occurs. Integration of HPV DNA into the basal epithelial cells leads to immortalization and rapid cellular turnover. This disordered immaturity within the epithelium is called ‘cervical intraepithelial neoplasia’ (CIN) and is truly an intraepithelial condition (cancer is diagnosed when this process breaks the basement membrane). Immature cells are hyperchromatic with large nuclei, minimal cytoplasm and abnormal mitotic figures. CIN is classified as either low-grade (CIN 1) or highgrade disease (CIN 2 and 3), depending on whether the abnormal cells are seen in the bottom third or top two-thirds of the cervical epithelium, respectively




Abnormal Changes to Squamous Cells in the Cervix
LSIL
HSIL
CIN 1
CIN 2
CIN 3
normal squamous cells
mild
moderate
severe
carcinoma in situ
dysplasia

Natural history of CIN Regression and progression of CIN may occur. Spontaneous regression of low-grade disease is not uncommon and is likely to occur through the patient's own cell-mediated immunity. This is the argument for observational follow-up in patients with low-grade abnormality. High-grade disease is less likely to regress spontaneously and requires treatment, as there is a risk of progression to cancer. If left untreated, around 20% of patients with high-grade abnormalities develop cancer of the cervix. Reasons for this remain unclear but may include high-risk HPV types, reduced host immunity and smoking. There is a convincing link between CIN and cancer of the cervix, as nearly all microscopic

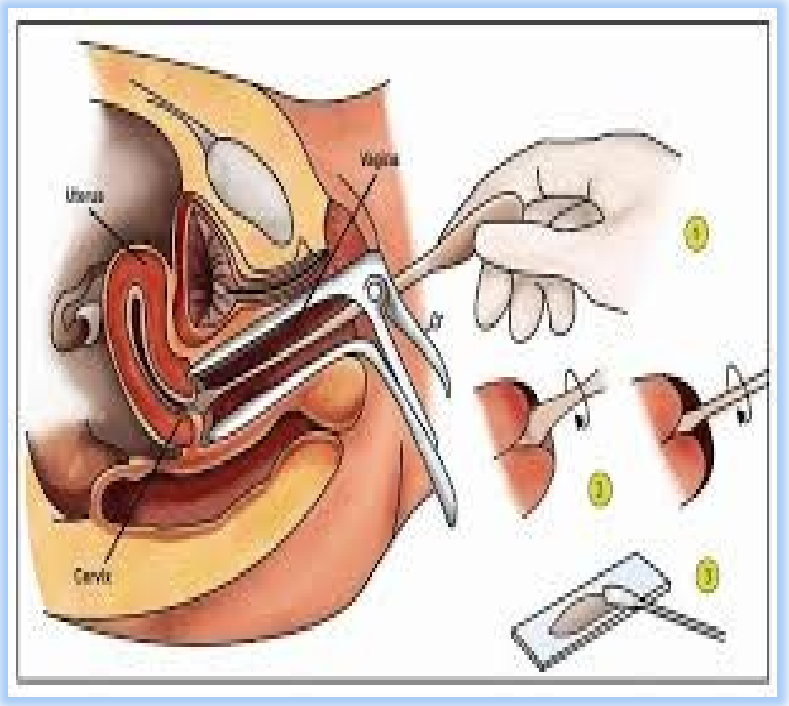
Diagnosis and investigations

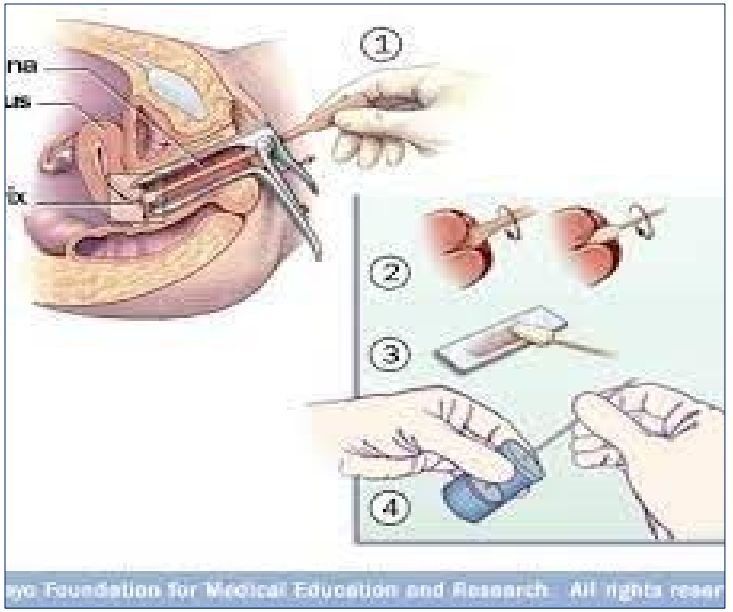
Cervical cytology Cells exfoliated from the cervix can be examined under the microscope and this acts as a good screening test. Originally the ‘Pap smear’ was introduced by Papanicolou, where cells were removed from the cervix using a wooden spatula and placed on a glass slide and fixed. The Pap smear has now been superseded by liquid-based cytology (LBC), whereby a small brush is used to sample cells from the TZ and the brush head placed in fixative. This is then spun down and the cellular aspect of the specimen examined under the microscope

- . For more than 95% of women, cervical cytology is normal and normal squamous cells are seen .Abnormal cervical cytology shows squamous cells at different stages of maturity (dyskaryosis). Like CIN, cervical cytology is classified as low grade (minor cytological abnormalities showing mild dyskaryosis or borderline change) or high grade (moderate and severe dyskaryosis) There is some correlation between the grade of cytological abnormality and the extent of CIN found on the cervix, but this is not totally reliable

. Cervical cytology triages patients to the colposcopy clinic for further assessment .The sensitivity of a single cervical smear for high-grade CIN detection is between 40% and 70%; however, as there is slow progression for most women with CIN to cancer, if a lesion is missed then this should be picked up on a subsequent test. Women who attend regularly for cervical cytology have a very low risk of developing cervical cancer.

Pap smear (cervical cytology)





The role of HPV testing in cervical screening High-risk HPV testing improves the sensitivity of cervical screening. Its value lies in its extremely high negative predictive power, which means that if a woman tests high-risk HPV negative, her risk of developing cervical cancer over the next 5–10 years is exceptionally low.

The majority of women (around 95%) have normal cervical cytology and are placed on routine recall.

Women with high-grade cytology (2%) are referred urgently for colposcopic assessment.

Women with minor cytological abnormalities undergo reflex testing with high-risk HPV. HPV-negative women are returned to routine recall, while high-risk HPV-positive women are referred for colposcopy.

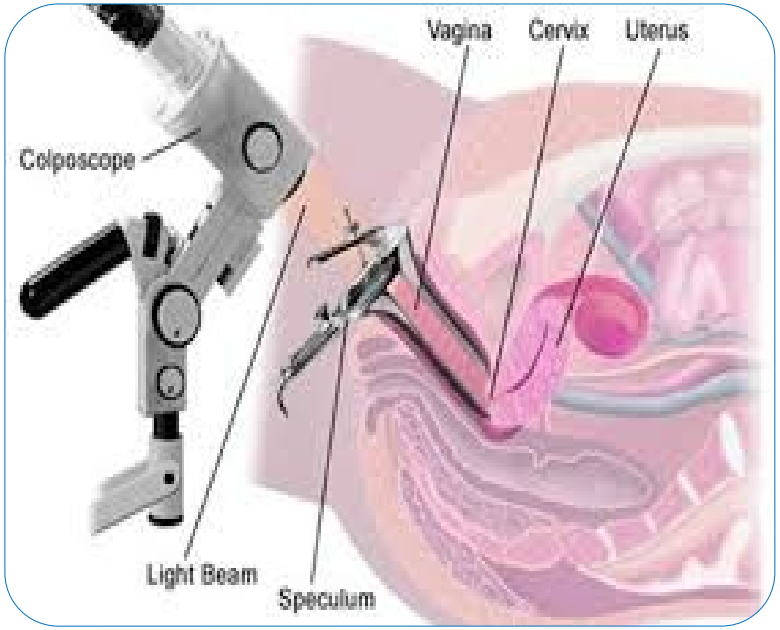
Many countries, including the UK, are now moving towards primary HPV screening; that is, testing all cervical cytology specimens for high-risk HPV first, and carrying out reflex cytological assessment on those that test positive. This will reduce the costs of the screening programme, since HPV testing is automated and achieves a high throughput, while cytological assessment is manual and requires a skilled workforce. The National Cervical Screening Programme Since 1988, the UK has offered population-based cervical screening. Women aged 25–64 are invited every 3–5 years to take part in the screening programme. Invitations for cervical screening and the handling of results are coordinated by the National Health Service Cervical Screening Programme (NHSCCP). The coverage in the UK is around 70–85% of the population

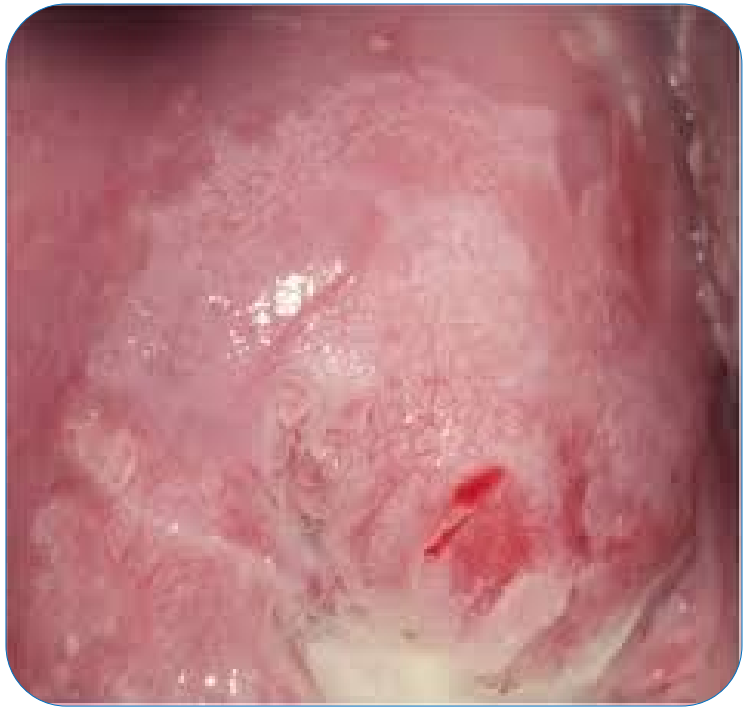
Colposcopy

Colposcopy is the examination of the magnified cervix using a light source It is used for both diagnosis and treatment. The woman undresses and places her legs in the semi-lithotomy position. A speculum is placed in the vagina and the cervix examined with a light source, under magnification (5–20-fold). The application of acetic acid and iodine solutions highlights abnormal areas of the cervix that can be biopsied. Acetic acid causes nucleoproteins within cells to coagulate temporarily; therefore, areas of increased cell turnover, including CIN, appear white .Areas of CIN lack intracytoplasmic glycogen and fail to stain brown when iodine is applied

CIN is a preneoplastic process and the process of angiogenesis (new blood vessel formation) is apparent in CIN when viewed through the colposcopy. If CIN is present, the colposcopist determines whether the appearances are low or high grade. The latter can be treated in the clinic on the same visit (known as ‘see and treat’); the former can be monitored with a subsequent colposcopy and cytology 6 months later. A biopsy usually helps make the decision if unsure (‘select and treat’).

Colposcopy





Treatment of premalignant disease of the cervix

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The aims of treatment are:

To effectively eradicate CIN,

Ensuring that post-treatment cytology is negative,

Minimizing harm to the patient from the treatment

High-grade CIN requires treatment, usually with excision or ablation. Low-grade CIN regresses spontaneously in up to 60% of cases; therefore, close follow-up with colposcopy and cytology 6 months after initial diagnosis is favoured as this avoids overtreating lesions that might have regressed.

The favoured method of treatment for highergrade CIN is loop diathermy (large loop excision of transformation zone, LLETZ). Under local anaesthetic, a diathermy wire loop is used to remove a portion of the cervix that includes the TZ with the area of CIN .CIN can develop within the crypts of the epithelium and therefore excisional techniques need to be at least 7 mm deep. The procedure takes 15 minutes under local anaesthetic.

The advantages of this excisional technique are that it is clinically effective (95% of patients have negative cytology at 6 months), cost-efficient (patients can be treated at the first hospital visit) and it provides a specimen for pathological assessment (1% of loop biopsies have an unsuspected microscopic cancer). The disadvantage relates to its potential impact on obstetric outcome. Small excisional treatments are unlikely to have obstetric consequences; however, if a large excision or repeat excisions remove a substantial proportion of the cervix, there is an increased risk of midtrimester miscarriage and preterm delivery in subsequent pregnancies. This concern relates to young women who have not completed their family.

Other options have been suggested for the treatment of CIN including cold coagulation and cone biopsy. The term ‘cold coagulation’ is a misnomer as the treatment involves placing a hot probe on the cervix in outpatients under local anaesthetic. It is a destructive treatment, is effective for both high- and low-grade CIN but does not provide a specimen. Cone biopsy involves cutting away a portion of the cervix under general anaesthetic and produces a specimen, like a LLETZ. Its disadvantage relates to the need for a general anaesthetic and 5% of patients may develop cervical stenosis or incompetence, which has obstetric implications. It has been largely superseded by loop diathermy.

Patients who have received treatment for CIN undergo a ‘test of cure’ 6 months later. This includes a high-risk HPV test and cytological assessment. If negative, the woman is returned to routine recall; that is, cervical screening in 3 years time. If positive, repeat colposcopy is indicated to identify any residual, untreated CIN. A woman with a history of CIN has an increased life-time risk of recurrent CIN and cervical cancer.

HPV vaccination

HPV vaccines have been shown to be safe and effective at preventing persistent high-risk HPV infection CIN. School-based immunization in the UK is aimed at 12–13-year-old girls so it will take many years to know if HPV vaccination can reduce deaths from cervical cancer. The bivalent vaccine prevents persistent infection with HPV types 16 and 18, which together are responsible for more than 70% of cases of cervical cancer. In 2011, the bivalent vaccine was replaced by the quadrivalent vaccine, which additionally protects against HPV types 6 and 11, the main perpetrators of genital warts. Uptake of the vaccine has been good (75–85%) and it is expected that this will result in fewer women being referred for colposcopy when they reach screening age. Current vaccination strategies are unlikely to result in the eradication of cervical cancer because other high-risk HPV types are not included and uptake is not universal. Future strategies will increase efficacy by vaccinating adolescent boys and the development of new polyvalent vaccines that provide protection against more high-risk HPV types.

Thank You.