

3. Management of Abnormal Cervical Smear

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Introduction

This guideline is to provide recommendations to aid General Practitioners and Gynaecologists on treatment of women with **Abnormal Cervical Smear**. This treatment could be initiated in a primary care setting or in centres with advanced facilities. The objectives of the guideline are early diagnosis, investigating, counselling and treatment of mother with abnormal cervical smear.

3.1. Scope of the guideline

Invasive cervical cancers are usually preceded by a long phase of pre-invasive disease. This is characterized microscopically as a spectrum of events progressing from cellular atypia to various grades of dysplasia or cervical intraepithelial neoplasia (CIN) before progression to invasive carcinoma. A good knowledge of the aetiology, pathophysiology and natural history of CIN provides a strong basis both for visual testing and for colposcopic diagnosis and understanding the principles of treatment of these lesions¹

3.1.1 Terminology²

As a result of advances in understanding of the pathogenesis of cervical cancer, the cervical intraepithelial neoplasia (CIN) terminology was introduced in the late 1980s (Richart, 1988, 1973). The CIN concept emphasized that dysplasia and carcinoma in-situ represent different stages of the same biological process, rather than separate entities. It had a major impact on how pre-cancerous lesions were treated, since all types of cervical cancer precursors were considered to form a biological and clinical continuum. In the CIN terminology, mild dysplasia is classified as CIN 1, moderate dysplasia as CIN 2 and

severe dysplasia and carcinoma in situ are grouped together and classified as CIN 3. The CIN terminology is still widely used in many countries for reporting both histological and cytological diagnoses.²

3.1.1.1 The Bethesda Systems of terminology²

By the late 1980s, advances in our understanding of the role of Human Papilloma virus (HPV) in the pathogenesis of cervical cancer needed to be incorporated into cytological terminology. Moreover, it was recognised that clinicians were often confused by the non-standard terminologies used to report cytological results and that this had a potential adverse impact on clinical care. Therefore, in 1988, the US National Institute of Health held a conference in Bethesda, Maryland, to develop a new terminology that would ensure better standardisation and accommodate current concepts of the pathogenesis of cervical disease, so that cytological findings could be transmitted to clinicians as accurately and concisely as possible. The terminology that resulted is known as **The Bethesda System**. In 1991 The Bethesda System was slightly modified on the basis of experience obtained during the first three years of its use and it was further modified in 2001 to take into account the results of new research and over a decade of experience with the terminology (Luff, 1992; Solomon et al, 2002).²

Consensus was reached to adopt The Bethesda System in Sri Lanka by The College of Pathologist and The Sri Lanka College of Obstetricians and Gynecologists in 2001.

The 2001 Bethesda system²

Specimen adequacy

- Satisfactory for evaluation (*note presence/ absence of endocervical transformation zone component*)
- Unsatisfactory for evaluation (*Specify reason*)
 - Specimen rejected (*Specify reason*)
 - Specimen processed and examined, but unsatisfactory for evaluation of epithelial abnormality because of (*Specify reason*)

General categorization

- Negative for intraepithelial lesions or malignancy
- Epithelial cell abnormality
- Other

Interpretation /Result

- Negative for intraepithelial lesions or malignancy
- Organisms
 - Trichomonas vaginalis*
 - Fungi organisms morphologically consistent with *Candida* specimens
 - Shift in flora suggestive of bacterial vaginosis
 - Bacteria morphologically consistent with Actinomyces species
 - Cellular changes consistent with Herpes simplex virus
- Other non-neoplastic findings (Optional to report; List not comprehensive)
 - Reactive cellular changes associated with inflammation (includes typical repair), radiation, and intrauterine contraceptive device.
 - Glandular cell status posthysterectomy
 - Atrophy

Epithelial cell abnormalities

- Squamous cell
 - Atypical squamous cell (ASC)
 - Of undermined significance (ASCUS)
 - Cannot exclude HSIL (ASC-H)
 - Low-grade squamous intraepithelial lesion (LSIL)
 - High-grade squamous intraepithelial lesion (HSIL) (Can use modifiers to separate into CIN 2 and CIN 3)
 - Squamous cell carcinoma
- Glandular cell
 - Atypical glandular cells (AGC)(specify endocervical, endometrial or not; otherwise specified)
 - Atypical glandular cells, favour neoplastic (specify endocervical or not; otherwise specified)
 - Endocervical adenocarcinoma *in situ* (AIS)
 - Adenocarcinoma

Other (List not comprehensive)

Endometrial cells in a woman \geq 40 years of age

From Solomon et al.

There are three distinct parts to each Bethesda System report:

- A statement of the specimen adequacy
- A general categorization
- A descriptive diagnosis.

These categories assist clinicians by providing answers to three basic questions:

- i. Do I need to repeat the cervical cytology?
- ii. Was the cervical cytology normal?
- iii. If the specimen was not completely normal, what specifically was wrong?

Because cervical cytology is considered a screening, rather than diagnostic test, the 2001 Bethesda System reports cytological findings as an ‘interpretation’ or ‘result’ rather than as a ‘diagnosis’ (cf: CIN Classification). This stresses the fact that cytological findings usually need to be interpreted in the light of clinical findings, and that the test is designed to reflect the underlying disease state but does not always do so.

3.1.1.2 Comparison of the WHO, CIN and Bethesda system terminology²

World Health Organization	CIN	Bethesda System
Normal		ASC (ASCUS/ ASC-H)
Mild dysplasia	CIN 1	LSIL
Moderate dysplasia	CIN 2	HSIL
Severe dysplasia	CIN 3	HSIL
Carcinoma in-situ	CIN 3	HSIL
Microinvasive carcinoma	Invasive carcinoma	Invasive carcinoma
Invasive carcinoma	Invasive carcinoma	Invasive carcinoma

(CIN, Cervical intraepithelial neoplasia; ASC, Atypical squamous cells; SIL, Squamous intraepithelial lesion)

3.2 Clinical considerations

Regression, persistence and progression probabilities of CIN/SIL (natural history)¹

Table 1.

CIN category	Regression	Persistence	Progression to CIN 3	Progression to invasive cancer
CIN 1	57%	32%	11%	1%
CIN 2	43%	35%	22%	1.5%
CIN 3	32%	50%	-	12%

Table 2.

Baseline cytological abnormality	Regression to normal at 24 months	Progression to HSIL at 24 months	Progression to invasive cancer at 24 months
ASCUS	88.2%	7.1%	0.3%
LSIL	47.4%	20.8%	0.2%
HSIL	35.0%	23.4% persistence	1.4%

3.3 Diagnosis

3.3.1 Colposcopy³

Colposcopy is the visual examination of the cervix using a low powered microscope known as a colposcope. It facilitates both the diagnosis and treatment of cervical intraepithelial neoplasia (CIN) and aids diagnosis of invasive cervical carcinoma.

Colposcopy enables abnormal areas of the cervix to be examined and guides the location of biopsies for histological diagnosis. The colposcope is used to visualise the cervix during treatment using a range of treatment methods.

This is primarily an outpatient based diagnostic and treatment service for women whose cervical smears have been abnormal or unsatisfactory. As such it plays a vital role in The Cervical Screening Programme. The success of the programme is also dependant upon high quality colposcopy services and upon appropriate links between Colposcopy, Laboratory Services (Cytology and Histology) and Primary Care.

Colposcopy guided treatment can be up to 90-95% effective.³

3.3.1.1 Guidelines for referral for colposcopy³

Women should be referred for colposcopy;

- After three consecutive inadequate samples. **(Grade X)**
- After three tests reported as borderline nuclear change in squamous cells in a series, without the woman being recalled to routine recall. **(Grade X)**
- After one test reported as borderline nuclear change in endocervical cells. **(Grade X)**
- If they have had 3 tests reported as abnormal at any grade in a 10 year period, even if returned to routine recall on one or more occasions in that period. (In the absence of symptoms a smear should be taken no sooner than 12 months after the first reported abnormal test). **(Grade X)**
- After two tests reported as mild dysplasia /LSIL without a return to routine recall. **(Grade X)**
- After one test reported as moderate dysplasia /HSIL.
- After one test reported as severe dysplasia /HSIL. **(Grade X)**
- After one test reported as possible invasion. They should be seen urgently within two weeks of referral. **(Grade X)**
- After one test reported as glandular neoplasia. They should be seen urgently within two weeks of referral. **(Grade X)**
- If they have been treated for CIN and have not been returned to routine recall and a subsequent test is reported as mild dysplasia or worse. **(Grade X)**

3.3.1.2 The colposcopic examination (step-by-step¹)

It is important to explain the examination procedure and reassure the woman before colposcopy. This will ensure that woman relaxes during the procedure.

(Grade X)

Written informed consent should be obtained from the woman before the colposcopic examination. **(Grade X)**

Relevant medical and reproductive history should be obtained before the procedure. **(Grade X)**

A strict adherence to the essential steps involved in colposcopic examination ensures that common errors are avoided.

It is important to visualize the squamo-columnar junction in its entire circumference; otherwise the colposcopic procedure is termed 'unsatisfactory'.

One should identify the transformation zone (TZ) during the colposcopic procedure. The proximal limit of the TZ is defined by the squamo-columnar junction, while the distal limit of the transformation zone is identified by finding the most distal crypt openings, nabothian follicles in the lips of the cervix and by drawing an imaginary line connecting these landmarks.

It is essential to obtain directed biopsies (B_x) under colposcopic control, from abnormal / suspicious areas identified. **(Grade X)**

Colposcopy during pregnancy requires considerable experience. As pregnancy progress cervical biopsy is associated with increased probability and severity of bleeding, which is often difficult to control. The risk of biopsy should always be weighed against the risk of missing an early invasive cancer. Non-invasive lesions may be evaluated post-partum.

3.4 Management

3.4.1 Components of management

3.4.1.1 Management of atypical squamous cells of undetermined significance (ASC-US)³

ASC frequency and association with CIN

- Average frequency of ASC: 4.4 %
- Associated CIN 2 or CIN 3: 5 - 17 %
- ASC assoc. with cervical carcinoma: 0.1 - 0.2 %

i. Acceptable Options:

- Follow-up with repeat cervical cytology in □ and 12 months; if ASC-US or more severe, refer to colposcopy.
- Perform HPV DNA testing for "high-risk" HPV types;

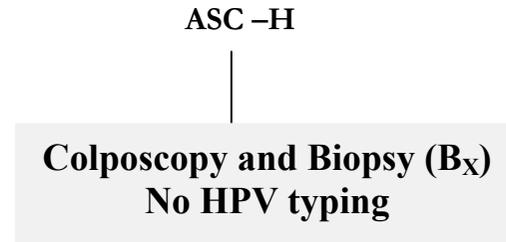
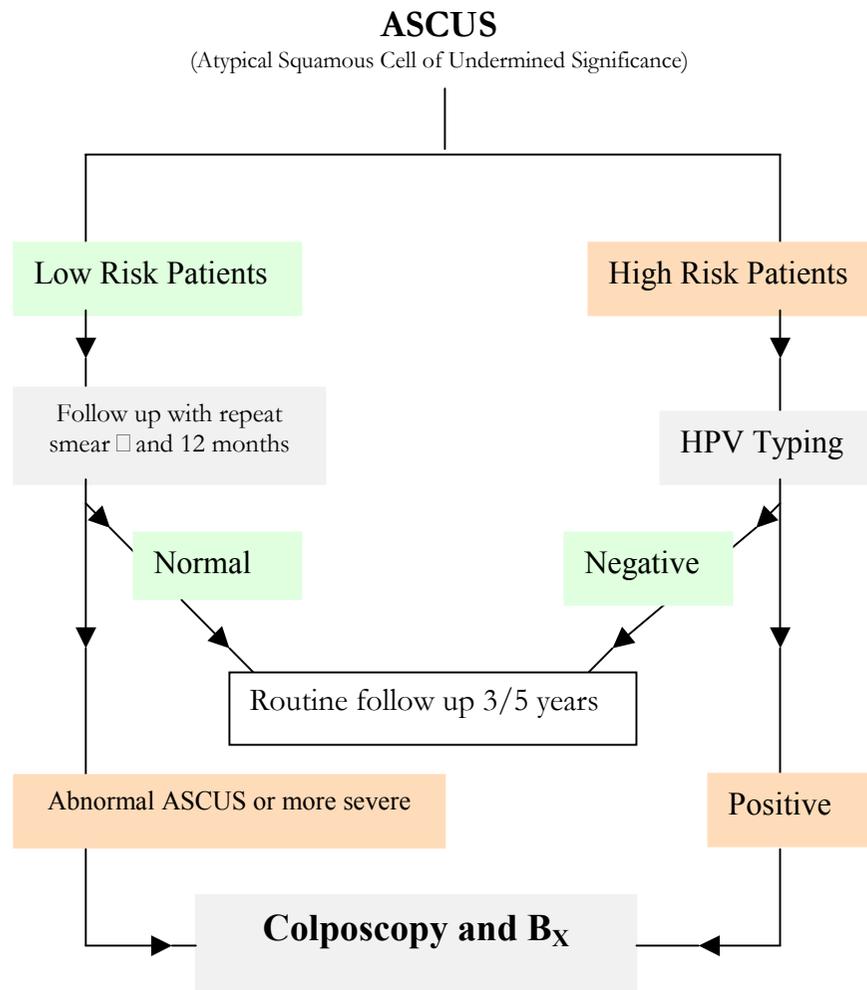
- **If HPV negative:** return to screening in 12 months

- **If HPV positive:** repeat cervical cytology in □ & 12 months,

If ASC-US or more severe, refer for colposcopy.

3.4.1.2 Management of ASC-H³ [Atypical Squamous Cell-cannot exclude High-grade squamous intraepithelial lesion (HSIL)]

- ASC-H (cannot exclude HSIL): Association with CIN 2 or CIN 3
- ASC overall: Associated with CIN 2 or CIN 3: 5 - 17 %
- ASC-H: Associated with CIN 2 or 3: 24 - 94 %
- Refer directly for colposcopy
Do not perform HPV testing
- ASC Special Circumstances;
 - Postmenopausal Women -Using intravaginal estrogen followed one week later with Pap smear → If (-ve), then repeat □ months later,
 - Immunosuppressed Women - Colposcopy referral is recommended,
 - Pregnant Women - Same as non-pregnant.



3.4.1.3 Management of LSIL³ (Low-grade Squamous Intraepithelial Lesion)

15%- 20% of women with SIL on cervical cytology will have CIN 2-3 identified on subsequent cervical biopsy

HPV DNA and **LLETZ** do not appear to be useful for the initial management of women with **LSIL**

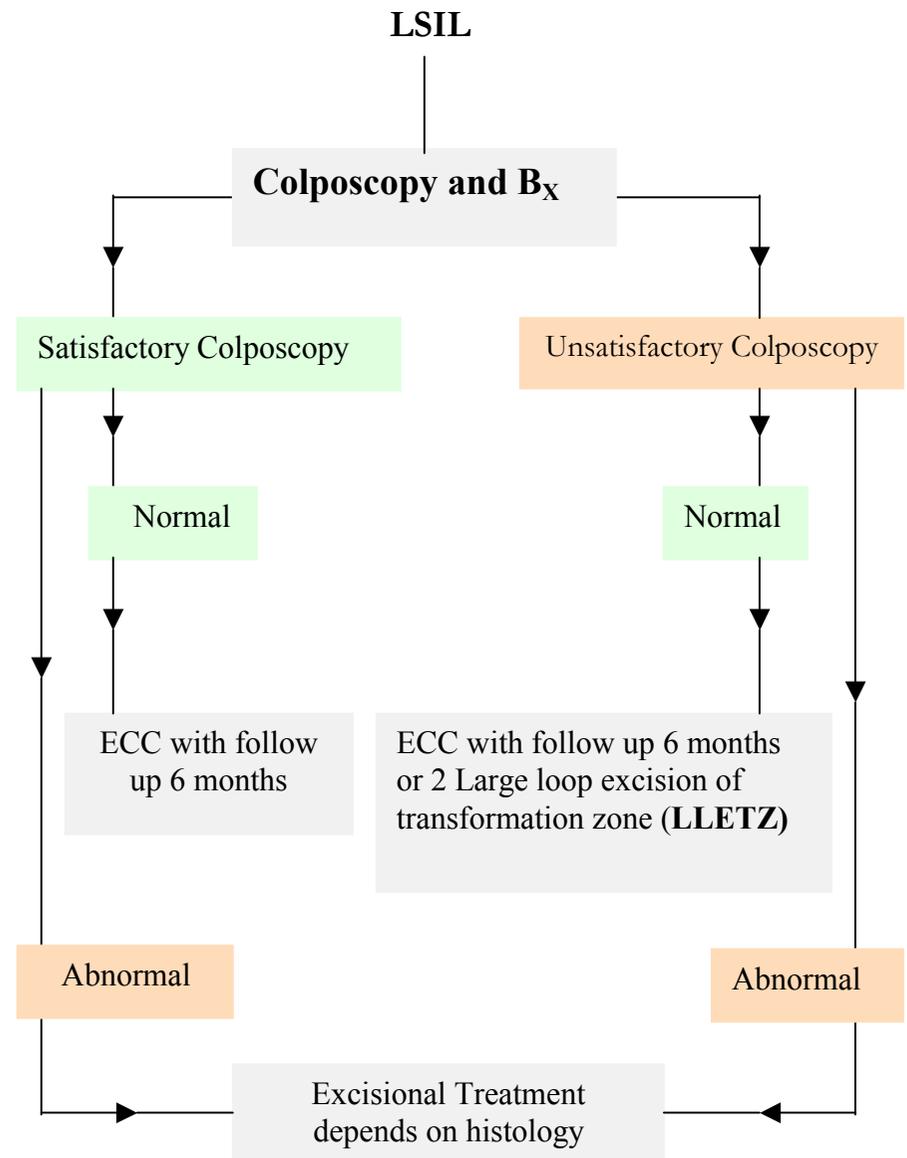
* Colposcopy with directed biopsies is the initial best option.

Satisfactory colposcopy – Endo-cervical cytology (ECC) is an acceptable option with follow up in □ months if normal.

Unsatisfactory colposcopy: ECC in non-pregnant with follow up in □ months if normal or directly LLETZ.

Pregnancy - Colposcopy with biopsy only if high grade lesion or cancer is suspected.

Adolescents - Acceptable option is, follow up in □ months without colposcopy.



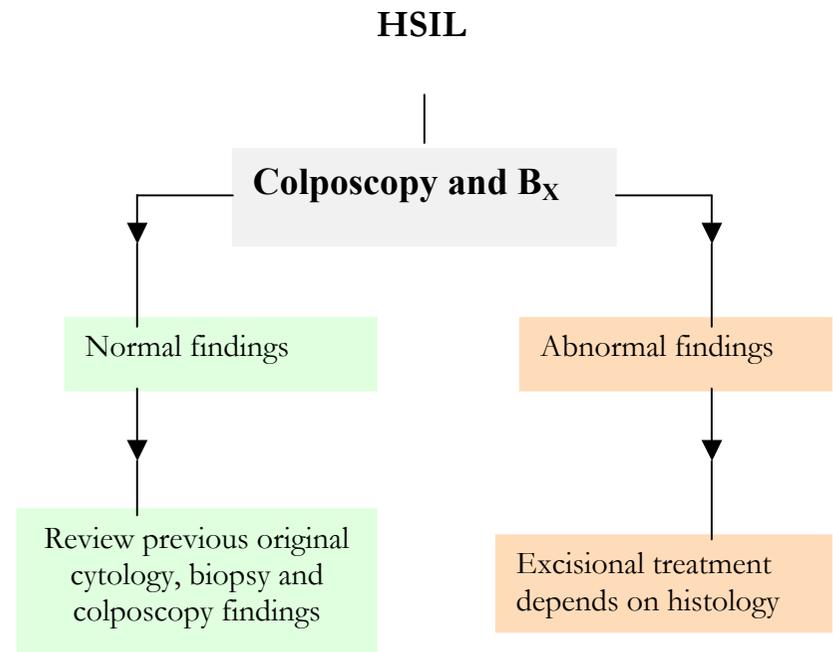
3.4.1.4 Management of HSIL [□] (High-grade Squamous Intraepithelial Lesion)

HSIL frequency and association with CIN

- Mean frequency of HSIL: 0.45 %
- Associated CIN 2 or CIN 3: 70 - 75 %
- HSIL assoc. with cervical carcinoma: 1 - 2 %

*** Recommended options:**

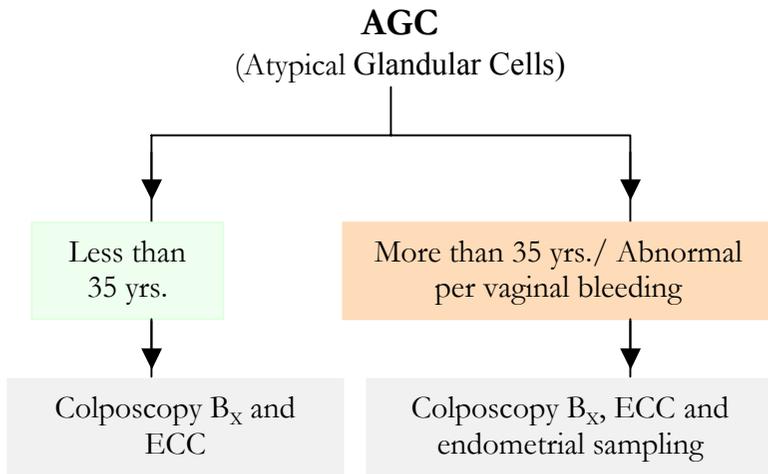
- Refer directly to colposcopy,
- If colposcopy and biopsies fail to identify CIN, review of the original cytology, biopsy and colposcopy findings are recommended,
- If the above review confirms HSIL, a diagnostic excisional procedure, such as electro-loop excision of the transformation zone is recommended in non-pregnant patients,



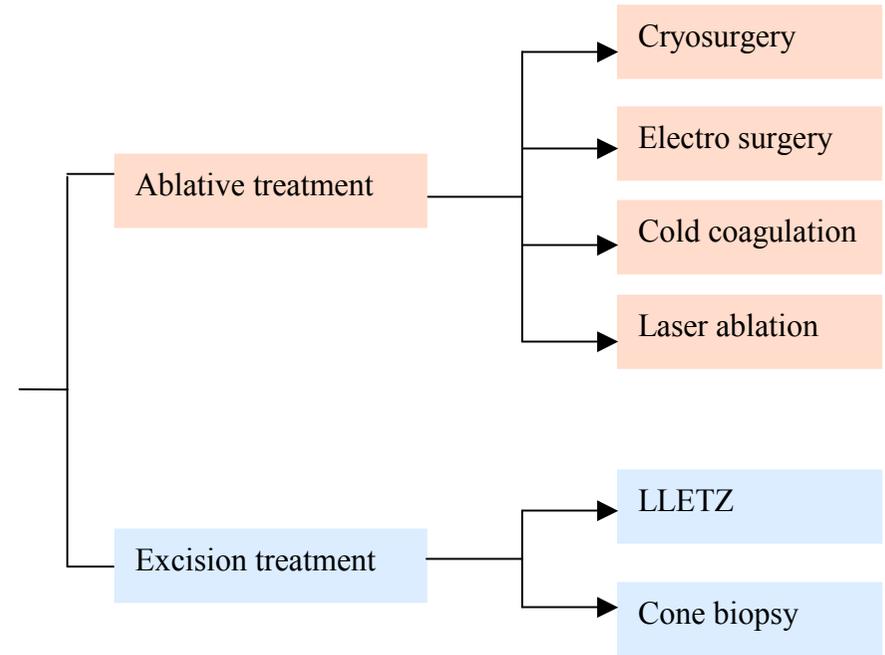
3.4.1.5 Management of glandular abnormalities (AGC) ³

- i. Reporting of any abnormal glandular sample must be supplemented by a written descriptive cytology report. **(Grade X)**
- ii. Colposcopy and endo-cervical cytology (ECC) is recommended for women with all subcategories of AGC with the caveat that women with atypical endometrial cells should have an endometrial biopsy, (EmB_x).
- iii. Postmenopausal women with atypical endometrial cells on a sample must be referred to a Gynaecologist. **(Grade X)**

- iv. Endometrial Biopsy (EmB_x) should be performed in conjunction with colposcopy in women older than 35 years with AGC and in younger women with AGC with unexplained bleeding or adenocarcinoma in situ (AIS).
- v. There is insufficient data to allow an assessment of HPV DNA testing in the management of women with AGC or AIS.



3.4.2 Methods of treatment



3.4.2.1 Cryotherapy¹

(Grade Z)

- i. Cryotherapy is suitable and an effective treatment option for CIN in both low- and high resource settings, as it requires less financial investment for equipment and maintenance.
- ii. Cryotherapy relies on a steady supply of compressed refrigerant gases (N₂O or CO₂) in transportable cylinders. Cryotherapy is not adequate to treat lesions involving the endocervix.
- iii. If excellent contact between the cryoprobe tip and the ectocervix is achieved, N₂O – based cryotherapy will achieve – 89^o C and CO₂ – based system will achieve – 8^o C at the core of the ice ball and temperatures around – 20^o C at the edges. Cells reduced to – 20^o C for one or more minutes will undergo cryonecrosis.
- iv. Healing takes place throughout the first 4 weeks after cryotherapy. Women may experience watery vaginal discharge for 3-4 weeks after treatment.
- v. Women should be advised not to use vaginal douches, tampons or have sexual intercourse for one month after treatment. Cryotherapy may increase the transmissibility of HIV infection and using condoms is an effective means of prevention.
- vi. **Treatment failure is observed in about 5-10 % of women.**

A. Eligibility criteria for cryotherapy.¹ (Grade X)

- i. The entire lesion is located in the ectocervix without extension to the vagina and /or endocervix,
- ii. The lesion is visible in its entire extent and does not extend more than 2 to 3 mm. into the canal,
- iii. The lesion can be adequately covered by the largest available cryotherapy probe (2.5 mm),
- iv. There is no evidence of invasive cancer,
- v. The endocervical canal is normal and there is no suggestion of glandular dysplasia,
- vi. The woman is not pregnant,
- vii. If the woman has recently delivered, she is at least three months post- partum,
- viii. There is no evidence of pelvic inflammatory disease,
- ix. The woman has given informed written consent to have the treatment.

4.2.2 Large loop excision of transformation zone (LLETZ)¹

- The key advantage of LLETZ over cryotherapy is that it removes rather than destroys the affected epithelium, allowing histological examination of the excised tissue.
- A loop wider than the lesion and the transformation zone to be removed should be used; otherwise, the lesion should be removed with multiple pieces.
- If the lesion involves the endocervical, a two-layer excision method should be used.

Woman will have a brown or black discharge for up to two weeks after LLETZ.

- Woman should be advised not to use vaginal douches, tampons, or have sexual intercourse for one month after LLETZ. **(Grade X)**
- Moderate to severe post-operative bleeding occurs in less than 2% of treated women and they should be seen promptly.
- The failure rate with LLETZ in woman treated for the first time is around 10%.

A. The eligibility criteria for LLETZ¹ (Grade X)

- i. CIN is confirmed by cervical biopsy, when possible.
- ii. If lesion involves or extended into the endo-cervical canal, the distal or cranial limit of the lesion should be seen; the furthest (distal) extent is no more than 1cm. in depth.
- iii. There is no evidence of invasive cancer or glandular dysplasia.
- iv. There is no evidence of pelvic inflammatory disease (PID), cervicitis, vaginal trichomoniasis, bacterial vaginosis, anogenital ulcers or bleeding disorders.
- v. If the woman has recently delivered, she should be at least three months post-partum.
- vi. Women with hypertension should have their blood pressure well controlled.

3.4.2.3 Cone biopsy¹

A. Indications

- The lesion extends into the endo-cervical canal and it is not possible to confirm the exact extent.
- The lesion extends into the canal and the farthest extent exceeds the excisional capability of the LLETZ technique (maximum excisional depth of 1.5 cm).
- The lesion extends to the canal and the farthest extent exceeds the excisional capability of the colposcopist.

- The cytology is repeatedly abnormal, suggesting neoplasia, but there is no corresponding colposcopic abnormality of the cervix or vagina on which to perform biopsy.
- Cytology suggests much more serious lesion than which is seen by biopsy when confirmed.
- Cytology shows atypical glandular cells that suggest the possibility of glandular dysplasia or adenocarcinoma.
- Colposcopy suggests the possibility of glandular dysplasia or adenocarcinoma.
- Endo-cervical curettage reveals abnormal histology.

B. Methods of cone biopsy:

- COLD KNIFE cone biopsy
- LEEP cone biopsy or LASER cone biopsy

3.4.3 Follow-up of women attending for colposcopy³

- i. All women remain at risk following treatment and must be followed up. **(Grade X)**
- ii. Follow-up should start at six months following treatment and not later than eight months following treatment. **(Grade X)**
- iii. All women who do not have negative test results after treatment must be re-colposcoped at least once within 12 months. **(Grade X)**
- iv. The proportion of confirmed histological treatment failures should not exceed 5% within 12 months of treatment.
- v. Biopsy should be undertaken in >95% of women with high grade abnormalities. **(Grade X)**
- vi. If at follow up a high grade cytological abnormality persists excisional treatment is recommended.

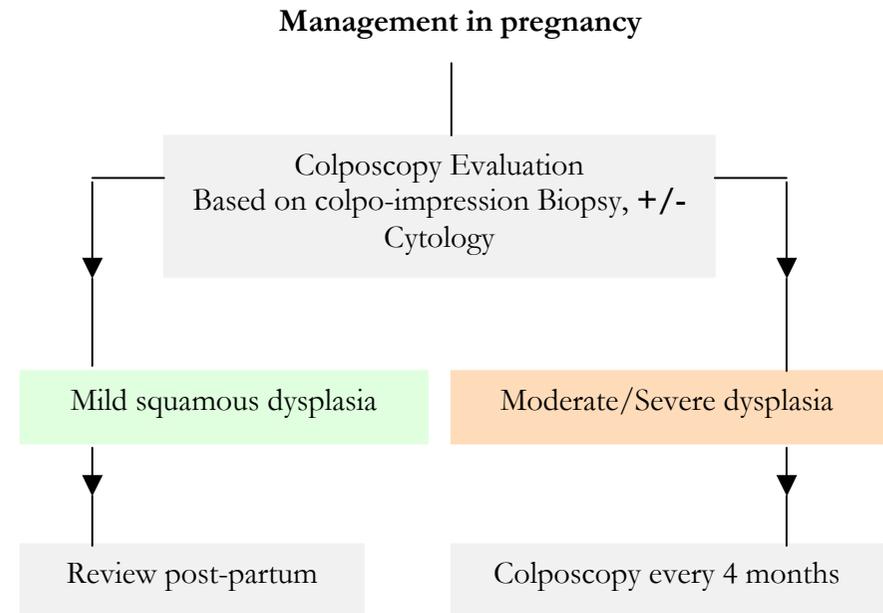
- vii. Women with mild dyskaryosis or less who have a satisfactory and normal colposcopic examination are at a low risk of developing cervical cancer. Their management is best determined by repeat cytological assessment six months after the referral sample:
 - If this is normal they can be returned to recall,
 - If this is borderline, repeat test in 12 months,
 - If this is mild dyskaryosis, a colposcopy with another test within 12 months is recommended
 - Any other test result warrants further colposcopy with or without biopsies,
- viii. Women referred with moderate dyskaryosis or worse cytological abnormalities who have a colposcopically low-grade lesion who are not treated, should have multiple biopsies

3.5 Special circumstances

3.5.1 Pregnancy, contraception, menopause and hysterectomy³

- i. If colposcopy has been performed during pregnancy, postpartum assessment of women with an abnormal cervical sample or biopsy proven CIN is essential. **(Grade X)**
- ii. Colposcopic evaluation of the pregnant woman requires a high degree of skill. If invasive disease is suspected clinically or colposcopically a biopsy adequate to make the diagnosis is essential. **(Grade X)**
- iii. The investigation of abnormal bleeding after the menopause must include direct visual inspection of the cervix. **(Grade X)**
- iv. All patients in the cervical screening age range undergoing a hysterectomy for other gynecological reasons should have a negative test result within the

- screening interval or as part of their preoperative investigations.
- v. All patients being considered for hysterectomy who have an undiagnosed abnormal sample or symptoms attributable to cervical cancer should have a diagnostic colposcopy and an appropriate biopsy. **(Grade X)**



- No treatment in pregnancy unless suspect invasion
- Cervical biopsy safe in pregnancy

3.5.2 Screening and management of immunosuppressed women³

- i. All patients who are immunosuppressed must be managed in a centre with demonstrable skills and expertise, with sufficient access to patient numbers to maintain that expertise.
- ii. All women aged 25–64 years with renal failure requiring dialysis must have cervical cytology performed at or shortly after diagnosis.

3.6 References

1. John W.Sellors, R Sankaranarayanan. Colposcopy and Treatment of Cervical Intraepithelial Neoplasia: A Beginners' Manual. WHO publication; 2003.
2. IARC Handbooks of Cancer Prevention, volume 10, Cervix, Cancer Screening; 2005.
3. G Doman, K Briggs. Northern Ireland Cervical Screening Programme, Colposcopic Standards Guideline

General Guidelines

Asepsis and Universal Precautions

Sepsis contributes significantly to maternal and neonatal morbidity and mortality. All possible efforts should be made to minimize sepsis during labour and surgical procedures.

Working in the labour suite, operating theatre exposes the labour room staff to the risk of infection following contamination with infected body fluids. Staff should take necessary precautions to safeguard themselves from such occupational hazards.

Recommendation

All steps in the management of labour and surgical procedures should be carried out under aseptic conditions. Members of the staff should adhere to universal precautions at all times.

(Grade X)

Documentation

Meticulous documentation of all events would improve the quality of patient care and will be useful for future reference. Fetal heart tracings and other relevant reports should be attached to the bed head ticket.

Recommendation

All steps in the management of labour and surgical procedures should be documented in the bed head ticket of the patient. Such records should have the time, the observations, any decisions made and the name of the responsible health care attendant.

(Grade X)

Quality assurance

Quality assurance is an integral part of maintaining a good health care delivery system. Measures taken on this regard would contribute to institutional development as well as improvement in the standard of care in the country.

Internal clinical audit, institutional conferences and basic research activities are useful in improving standards of an institution.

In-service training in relevant areas and opportunities for continuous medical education should be made available to all grades of staff.

Recommendation

Regular audit cycles of the quality of labour ward practices and operating theatre procedures should be an important aspect of the functions of an obstetric and gynaecological unit.

(Grade Y)