CervicalScreen Singapore

Management Guidelines for Abnormal Pap Smear & Preinvasive Disease of the Cervix

FOREWORD

Cervical cancer is the 4th most common cancer among women in Singapore. The incidence of cervical cancer has declined from 18.1 per 100,000 population for the years 1968-72 to 14.2 per 100,000 population between 1993-97. However, the incidence rate in Singaporean women remains higher than that of developed countries.

In 1998, the Ministry of Health set up the Cervical Cancer Screening Committee to develop an organised population-based cervical cancer screening programme to reduce cervical cancer mortality. It was recognised that evidence-based management guidelines were necessary for the evaluation and management of women with different grades of cervical abnormality detected by the cervical cancer screening programme. A workgroup, chaired by A/Prof Ho Tew Hong with representatives from the Chapter of Obstetrics & Gynaecology, Academy of Medicine, Singapore, Obstetrical & Gynaecological Society of Singapore, Society for Colposcopy & Cervical Pathology of Singapore, Singapore General Hospital, National University Hospital and KK Women's & Children's Hospital was formed to develop a set of management guidelines for handling abnormal Pap smears.

The *CervicalScreen Singapore: Management Guidelines for the Abnormal Pap Smear and for Preinvasive Disease of the Cervix* will be a useful guide for clinicians in the management of patients with abnormal Pap smears.

I would like to extend my sincere thanks to the workgroup for their commitment and hard work in developing the guidelines.

Dr Lam Sian Lian
Chief Executive Officer
Health Promotion Board

PREFACE

Whilst the incidence of cervical cancer in Singapore has decreased slightly in the last 25 years, much can still be done to reduce the rates of cervical cancer further.

The primary aim of the CervicalScreen Singapore Programme is to further reduce the incidence and mortality from cervical cancer through early detection. An important aspect of this Programme is to guide general practitioners on the management guidelines for screened cervical abnormalities.

A Workgroup consisting of representatives from Chapter of Obstetrics & Gynaecology, Academy of Medicine of Singapore, Obstetrical and Gynaecological Society of Singapore, the Society for Colposcopy and Cervical Pathology of Singapore, Singapore General Hospital, National University Hospital and KK Women's & Children's Hospital met on several occasions to work out consensus management guidelines for abnormal PAP smear and for preinvasive disease of the cervix. Views from international experts were sought and the consensus guidelines of Bethesda 2001 were also taken into account.

These consensus guidelines are formulated specifically for the purpose of the oncoming CervicalScreen Singapore Programme.

Ho Tew Hong
Clinical Associate Professor
Chairman of Workgroup
CervicalScreen Singapore:
Management Guidelines
for Abnormal Pap Smear and
Preinvasive Disease of the Cervix

CONTENTS

1 CERVICALSCREEN SINGAPORE

1. Age Group to be Screened and Screening Interval

1.1 Entry to Screening Programme

- All women who have ever had sex are advised to have their first Pap smear by the age of 25

1.2 Frequency of Screening

- Pap smears are taken once every 3 years

1.3 Discharge from Screening

- A woman can be discharged from screening at 65 years of age if the smear taken at 65 years is negative and there was a previous negative smear within the last 3 years

- However if a woman, who has had sexual intercourse, has never had a Pap smear, she should still undergo screening irrespective of her age

1.4 Women who have never had Sexual Intercourse

- Women who have never had sexual intercourse need not have Pap smear screening

- However if these women have any symptoms, they should consult a doctor

Note : Consider screening at an earlier age and at more frequent intervals if high risk characteristics are present. High risk characteristics include:

- Multiple sexual partners (either partner)
- Onset of sexual intercourse at an early age
- HPV infection
- History of STD
- HIV infection
- Immunosuppression
- Cigarette smoking

2 TERMINOLOGY FOR CERVICAL SMEAR REPORTING

(A) List of terminology

1. Unsatisfactory

2. Negative for Malignant Cells

3. Abnormal Smears

3.1 Squamous Lesions

3.1.1 Atypical Squamous Cells
- undetermined significance (ASC-US)
- cannot exclude high grade lesion (ASC-H)

3.1.2 Low-Grade Squamous Intraepithelial Lesion (LSIL)
- HPV effect
- mild dyskaryosis

3.1.3 High-Grade Squamous Intraepithelial Lesion (HSIL)
- moderate dyskaryosis
- severe dyskaryosis
- severe dyskaryosis, cannot rule out invasive carcinoma

3.1.4 Squamous Cell Carcinoma

3.2 Glandular Lesions

3.2.1 Atypical Glandular Cells
- undetermined significance
- favour neoplastic

3.2.2 Endocervical Adenocarcinoma-in-Situ

3.2.3 Adenocarcarcinoma

3.3 Others

3.3.1 Carcinoma
- others - specify
- not further specified

3.3.2 Other Malignant Tumours
- specify

(B) Definitions

- **Unsatisfactory**

  A smear that is unreliable for the detection of cervical epithelial cell abnormalities.

A satisfactory smear should show well-preserved and well-visualised squamous cells covering at least one-third of the area of a regular glass slide surface.

If fewer than these are seen because of paucity of cells, poor fixation, air- drying artefact, thick smearing, or covering of blood, inflammatory exudate or other contaminants, the smear is considered unsatisfactory.

A smear comprising mainly endocervical cells is also considered unsatisfactory, unless the smear was intended to specifically evaluate the endocervical canal.

• Negative for Malignant Cells

The smear shows no dyskaryotic or malignant cells ie. no cytological evidence of Cervical Intraepithelial Neoplasia (CIN), glandular dysplasia or malignancy.

This category includes those in which cells showing reactive changes are present, and also those in which micro-organisms are identified.

• Squamous Lesions

Atypical Squamous Cells

- undetermined significance
- cannot exclude high grade lesion

There are cells showing cytologic changes suggestive of a dysplastic squamous lesion that is quantitatively or qualitatively insufficient for a definitive interpretation.

Undetermined Significance (ASC-US)
Cytologic changes suggestive of a low grade squamous lesion but lack criteria for definitive interpretation.

Cannot Exclude High Grade Lesion (ASC-H)
Cytologic changes suggestive of a high grade squamous lesion but lack criteria for definitive interpretation.

Low-Grade Squamous Intraepithelial Lesion (LSIL)

- HPV effect
- mild dyskaryosis

HPV Effect
Squamous cells present showing stringent criteria of HPV effect ie. koilocytes in superficial or intermediate squamous cells or sharply delineated perinuclear halos in parabasal cells.

Mild Dyskaryosis
Cytologic changes indicative of CIN I.

High-Grade Squamous Intraepithelial Lesion (HSIL)

- moderate dyskaryosis
- severe dyskaryosis
- severe dyskaryosis, cannot rule out invasive carcinoma

Moderate Dyskaryosis
Cytologic changes indicative of CIN 2.

Severe Dyskaryosis
Cytologic changes indicative of CIN 3.

Severe Dyskaryosis, Cannot Rule Out Invasive Carcinoma
Cytologic changes indicative of at least CIN 3, but with features of possible invasive tumour.

Squamous Cell Carcinoma
Cytologic changes indicative of an invasive squamous cell carcinoma.

• Glandular Lesions

Atypical Glandular Cells
- undetermined significance
- favour neoplastic

There are cells showing cytologic changes suggestive of a dysplastic glandular lesion that are quantitatively or qualitatively insufficient for a definitive interpretation. Where possible, these are qualified as to whether the abnormal cells are of endocervical or endometrial origin.

Undetermined Significance
Cytologic changes which exceed those of a reactive process but lack criteria for a definitive interpretation of a dysplastic glandular lesion.

Favour Neoplastic
Cytologic changes suggestive of a glandular dysplasia or adenocarcinoma-in-situ or adenocarcinoma, but lack criteria for definitive interpretation.

Endocervical Adenocarcinoma-in-Situ
Cytologic changes indicative of endocervical adenocarcinoma-in-situ.

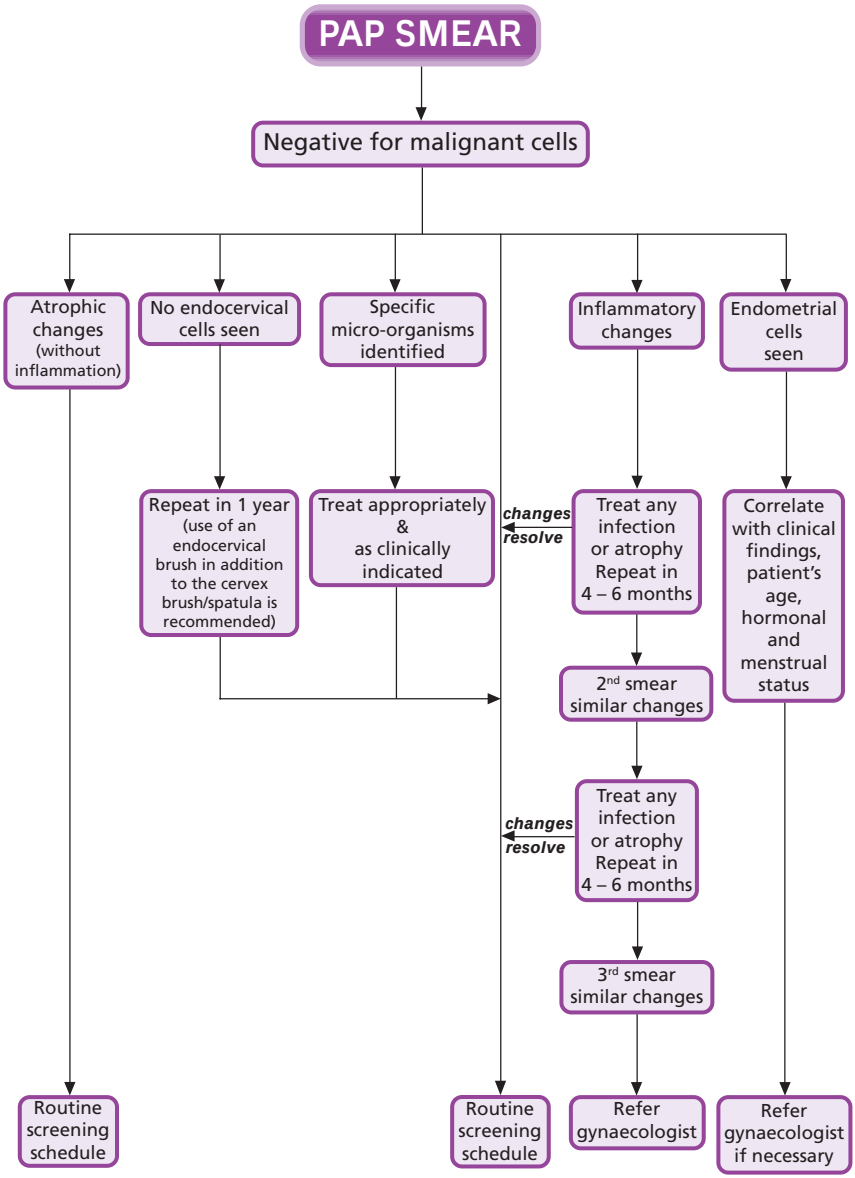
Adenocarcarcinoma
Cytologic changes indicative of an invasive adenocarcinoma.

• Others

Carcinoma
- others - specify
- not further specified

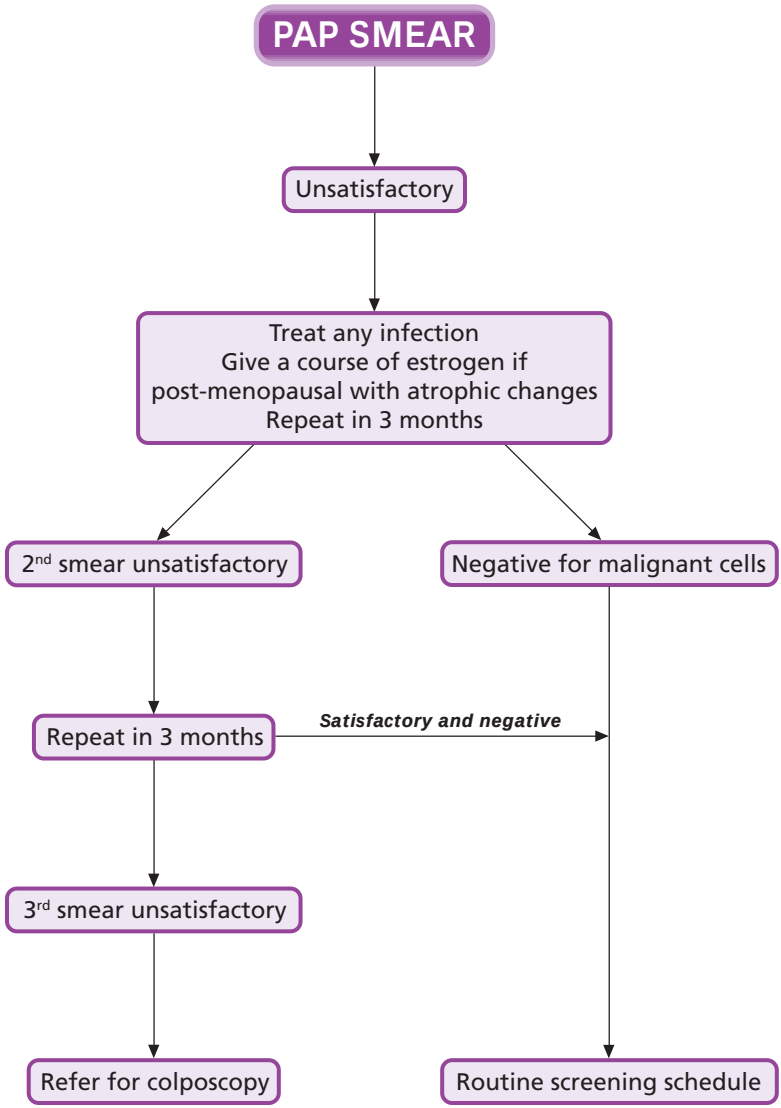
Other Malignant Tumours
- specify

3 MANAGEMENT PROTOCOL FOR "NEGATIVE FOR MALIGNANT CELLS" SMEARS



Note : Clinically suspicious looking cervix irrespective of the Pap smear result must be referred for colposcopy.

4 MANAGEMENT PROTOCOL FOR UNSATISFACTORY SMEARS

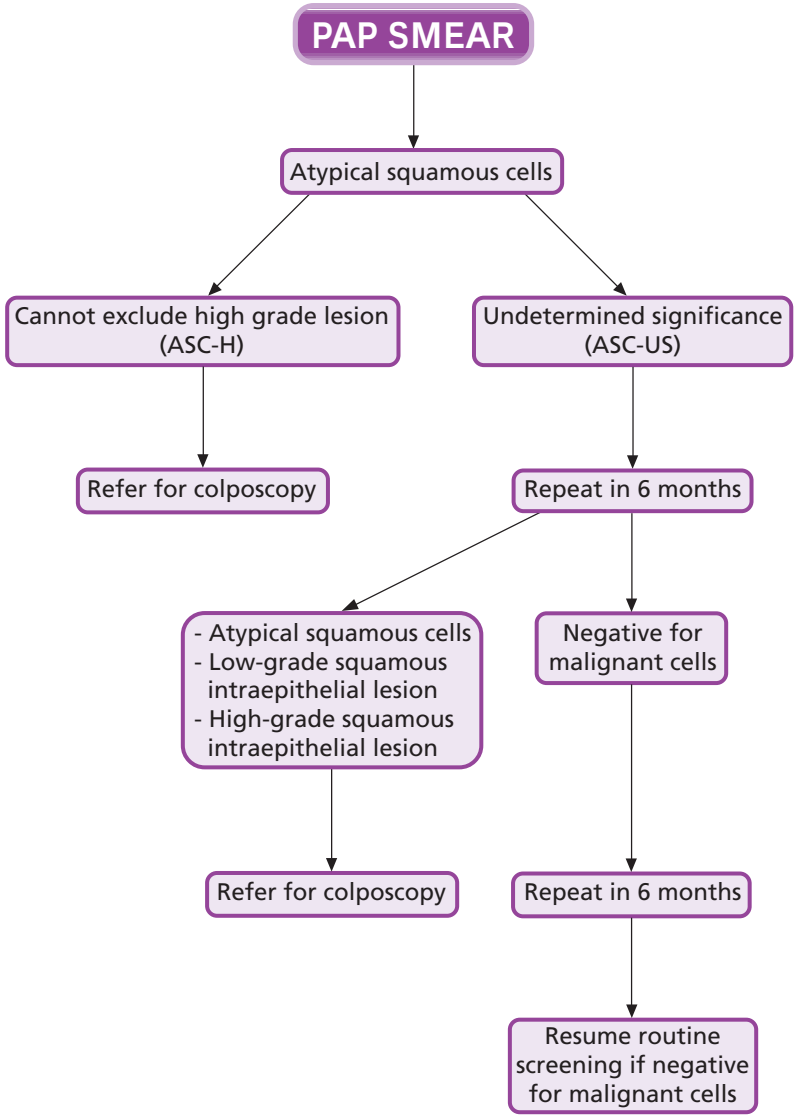


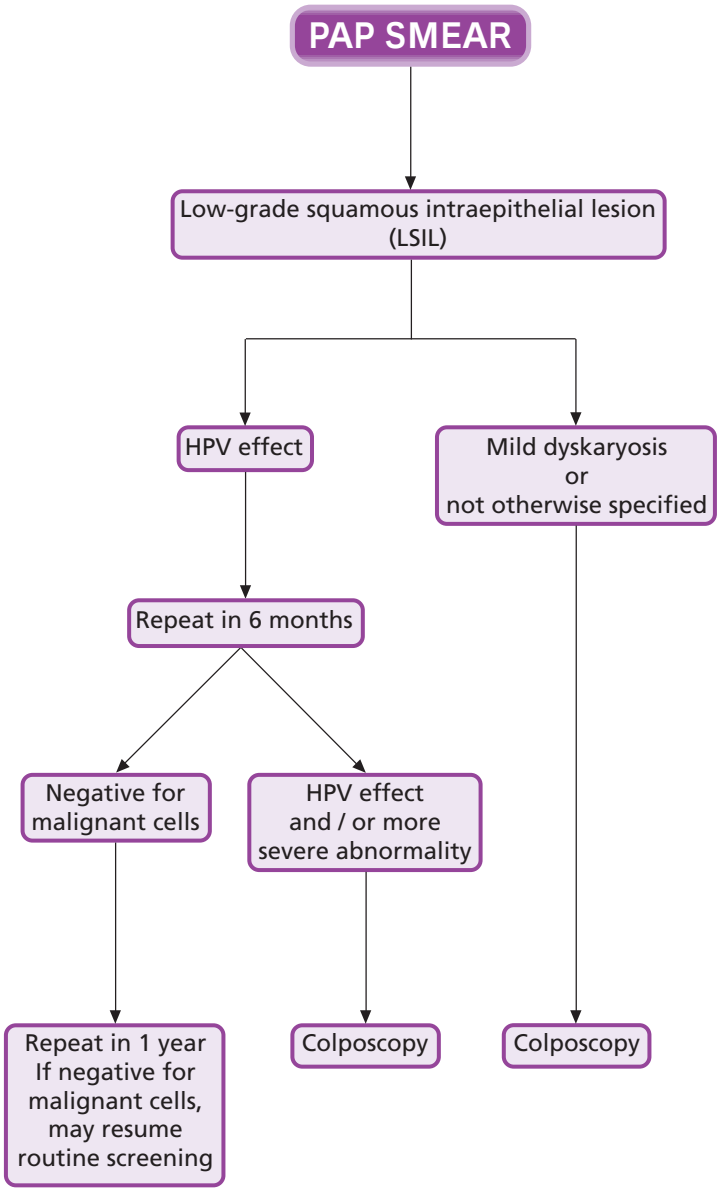
Note : Clinically suspicious looking cervix irrespective of the Pap smear result must be referred for colposcopy.

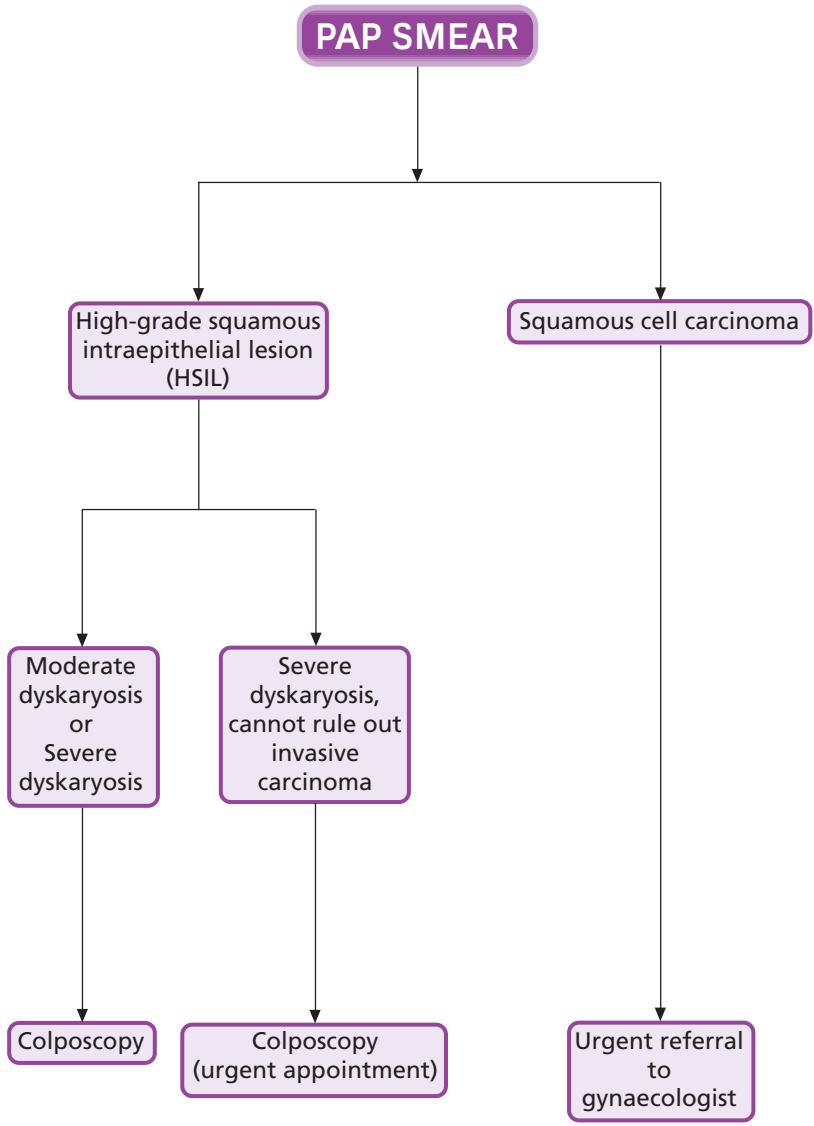
5 MANAGEMENT PROTOCOL FOR ABNORMAL SMEARS

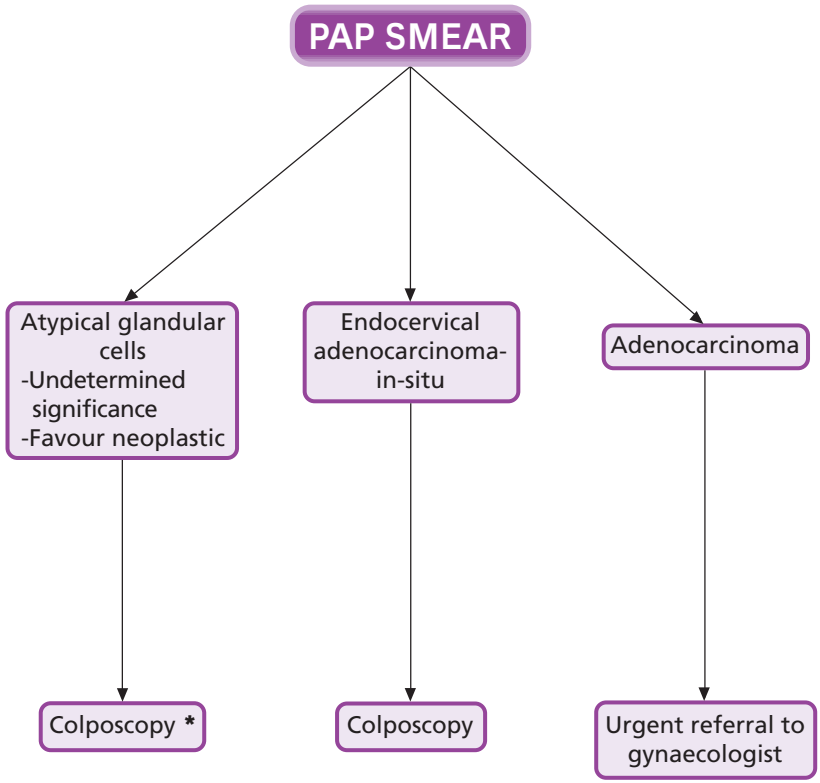
5.1 Management of Abnormal Smear

(No past history of CIN or genital tract cancer)

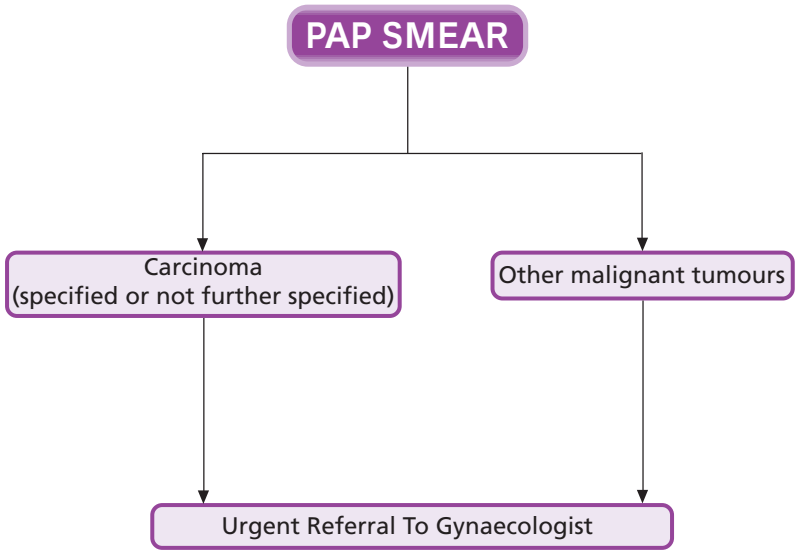



PAP SMEAR
Low-grade squamous intraepithelial lesion (LSIL)
HPV effect
Mild dyskaryosis or not otherwise specified
Repeat in 6 months
Negative for malignant cells
HPV effect and / or more severe abnormality
Repeat in 1 year If negative for malignant cells, may resume routine screening
Colposcopy
Colposcopy


PAP SMEAR
High-grade squamous intraepithelial lesion (HSIL)
Squamous cell carcinoma
Moderate dyskaryosis or Severe dyskaryosis
Severe dyskaryosis, cannot rule out invasive carcinoma
Colposcopy
Colposcopy (urgent appointment)
Urgent referral to gynaecologist



*Colposcopist to refer to management guidelines 8.3



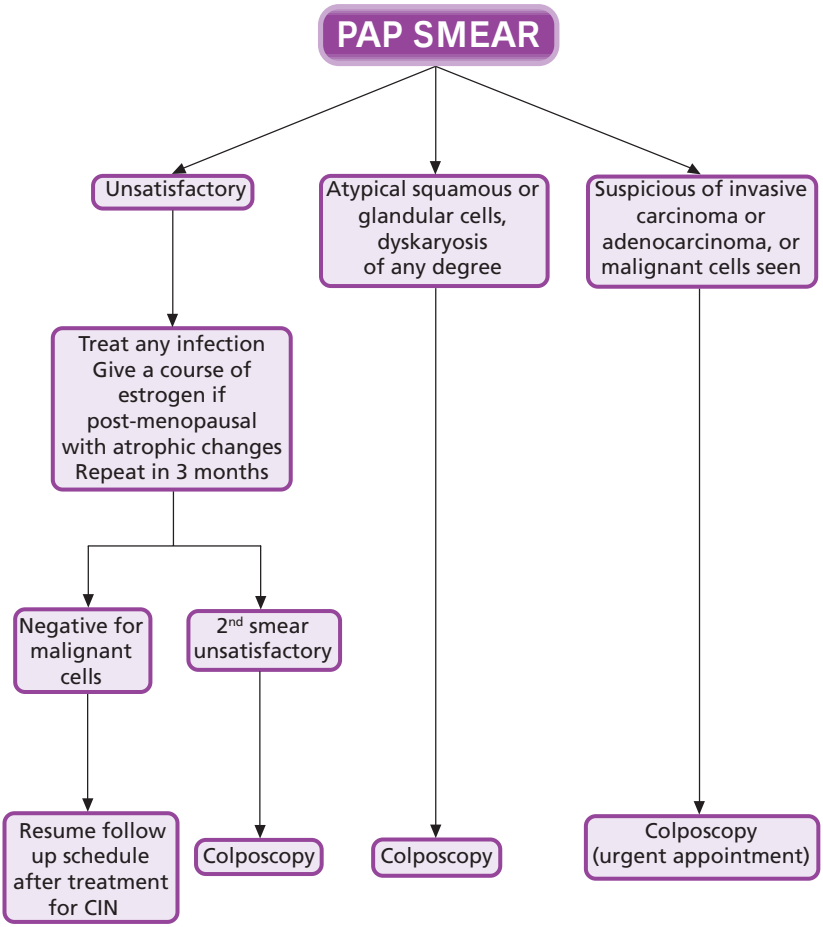
Other indications for referral :

a. Abnormal vaginal bleeding, eg. post-coital, post-menopausal or intermenstrual, should always be investigated and the woman referred for a specialist opinion.

b. Clinically suspicious looking cervix irrespective of the Pap smear result must be referred for colposcopy.

5.2 Management of Abnormal Smear

(Following treatment for CIN or CGIN)



5.3 Management of the Abnormal Smear in Pregnancy

The same as in the non-pregnant patient

6 PAP SMEARS AFTER HYSTERECTOMY

1. Hysterectomy for benign disease

   (a) Normal Pap smear history

   (b) Histopathology of cervix known and is benign with no dysplastic/ neoplastic changes

   - These women, in the absence of symptoms, need not have any further Pap smears

2. Subtotal hysterectomy

   Should continue to have Pap smears according to the screening programme

3. Hysterectomy where histology not known

   - One base-line Pap smear of vaginal vault
   - If this is normal, then no further smears are required

4. Immunosuppressed women (due to disease or therapy)

   - Should continue to have Pap smears of the vault at yearly intervals

5. Women with a past history of CIN

   (a) If excision margin was involved or not adequately assessed histologically

   - Follow up should be at the discretion of the gynaecologist
   - Vault smears should in general be taken at least yearly

   (b) CIN (CIN 1 / 2 / 3) completely excised at hysterectomy

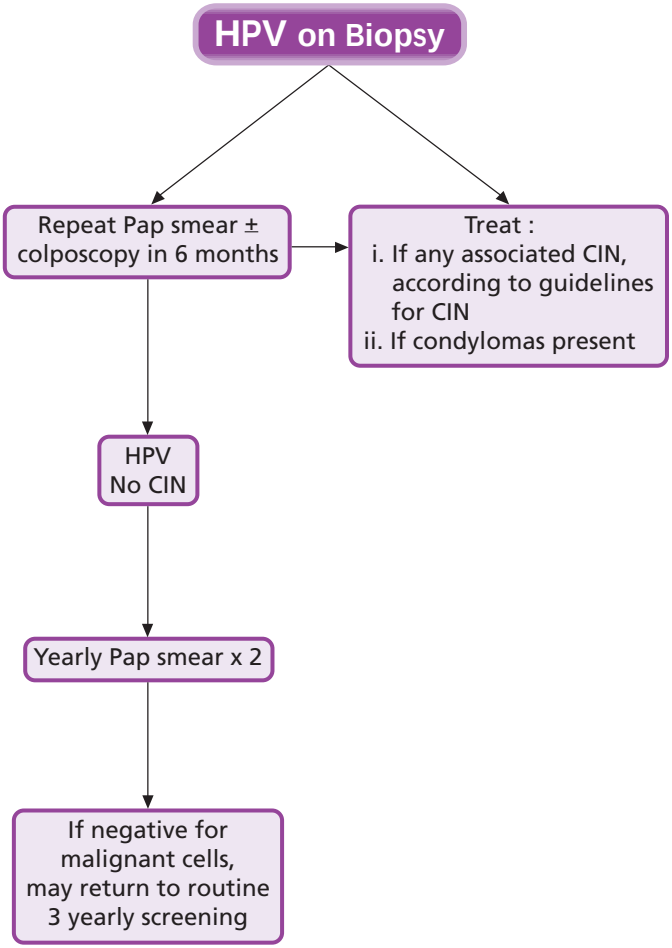
   - Vault smears for five years yearly
   - Two yearly subsequently

6. Women previously treated for VAIN, or invasive gynaecological malignancy

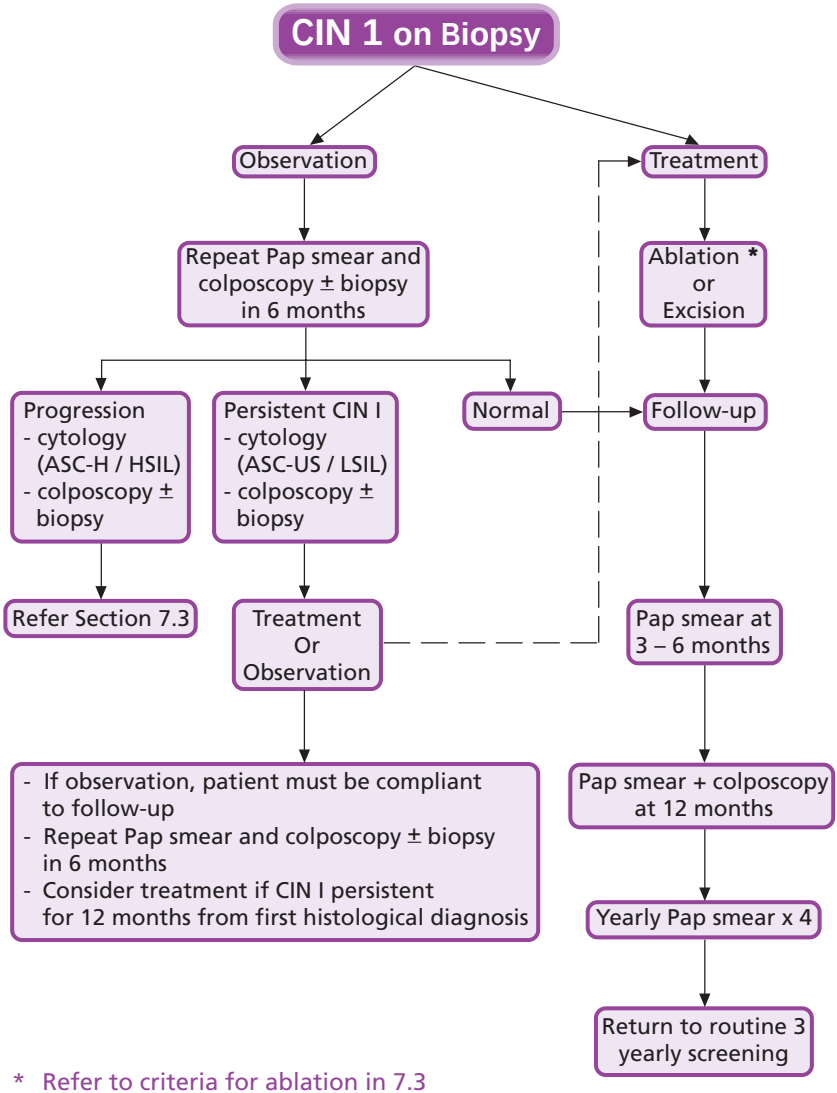
   - These women should be followed up by the treating gynaecologist/ gynaecological oncologist

7 MANAGEMENT OF PREINVASIVE DISEASE OF THE CERVIX

7.1 HPV


HPV on Biopsy
Repeat Pap smear ± colposcopy in 6 months
Treat :
i. If any associated CIN, according to guidelines for CIN
ii. If condylomas present
HPV No CIN
Yearly Pap smear x 2
If negative for malignant cells, may return to routine 3 yearly screening

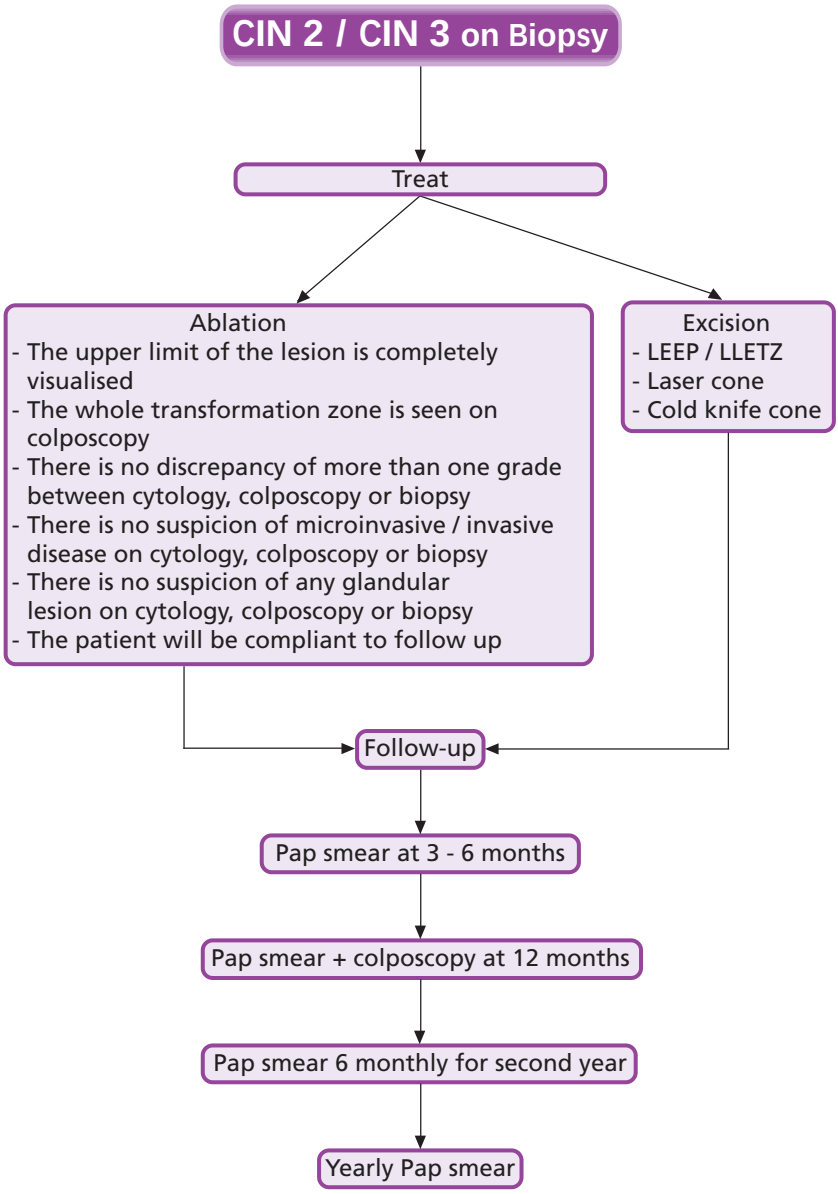
7.2 CIN 1



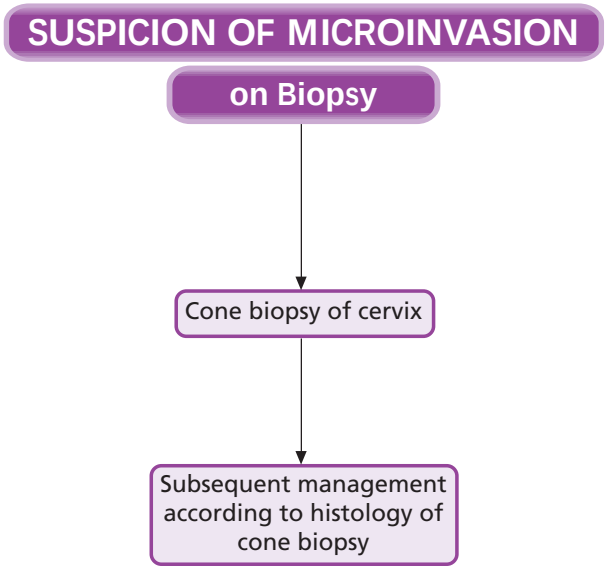
* Refer to criteria for ablation in 7.3

Note : The management of CIN I is controversial; patients can be managed by either observation or treatment.
If immunocompromised patient, suggest treatment as CIN less likely to regress.

7.3 CIN 2 and CIN 3

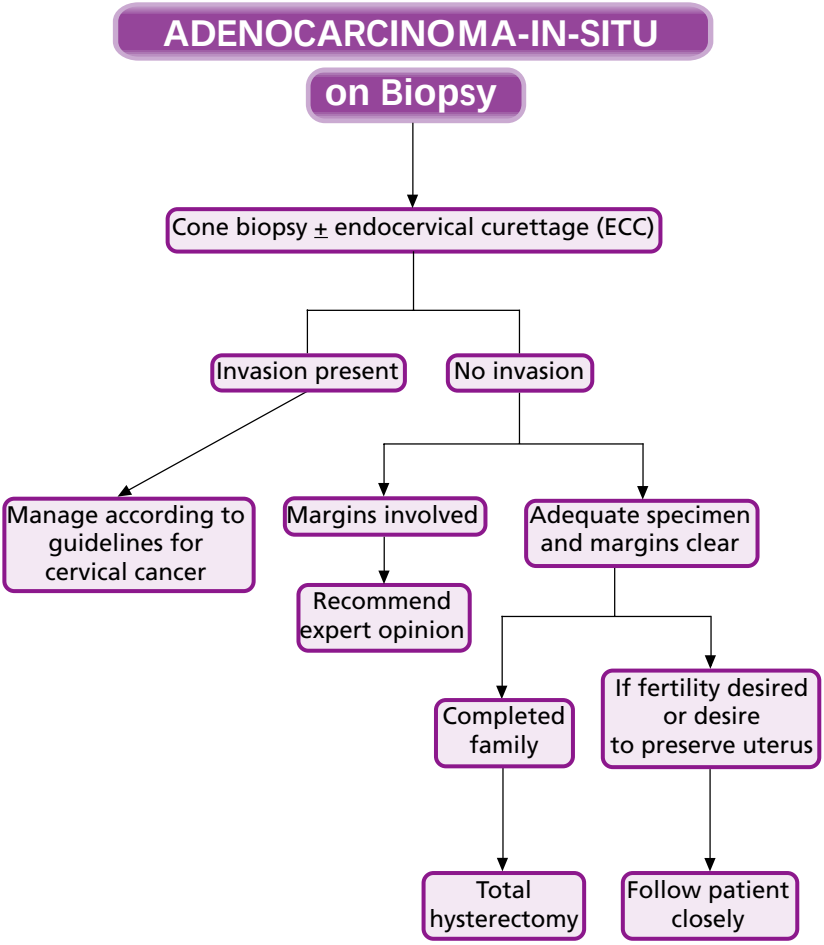


7.4 Suspicion of Microinvasion on Cervical Biopsy



Note : For suspected microinvasion a single large cone biopsy specimen with clear margins is necessary for adequate histopathological interpretation. A LEEP may not be adequate. A cold knife cone under anaesthesia is preferred.

7.5 Adenocarcinoma-in-situ



Note : For cone biopsy for adenocarcinoma-in-situ, a single large specimen with clear margins is necessary for adequate histopathological interpretation. A LEEP may not be adequate. A cold knife cone under anaesthesia is preferred.

7.6 Management of the Abnormal Smear and CIN in Pregnancy

1. Colposcopic evaluation should be undertaken to exclude invasive disease, by a colposcopist experienced in colposcopy in pregnancy.

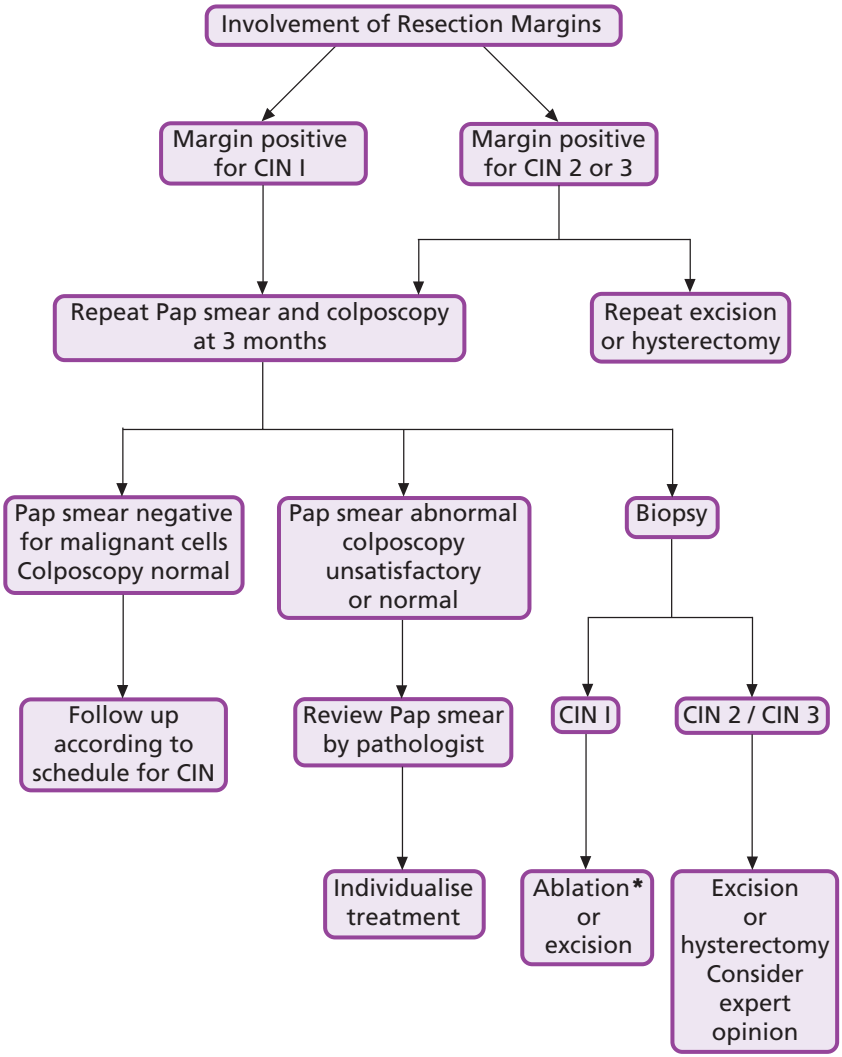
2. If a high grade lesion is suspected on colposcopy, a biopsy is indicated to exclude possible invasive disease. Cervical biopsy is safe in pregnancy.

3. If CIN 2 or 3 is present, colposcopic review should be done in the second or third trimester to exclude any possible progression to invasive disease.

4. Treatment of CIN should be deferred till at least 8 weeks post-partum, when the lesion should be reassessed. If the patient is breast feeding, local application of estrogen before the colposcopic reassessment may assist accurate evaluation.

Note : The management of labour is not influenced in any way by the presence of CIN, irrespective of severity.

7.7 Involvement of Margins after Cone Biopsy or LEEP for CIN



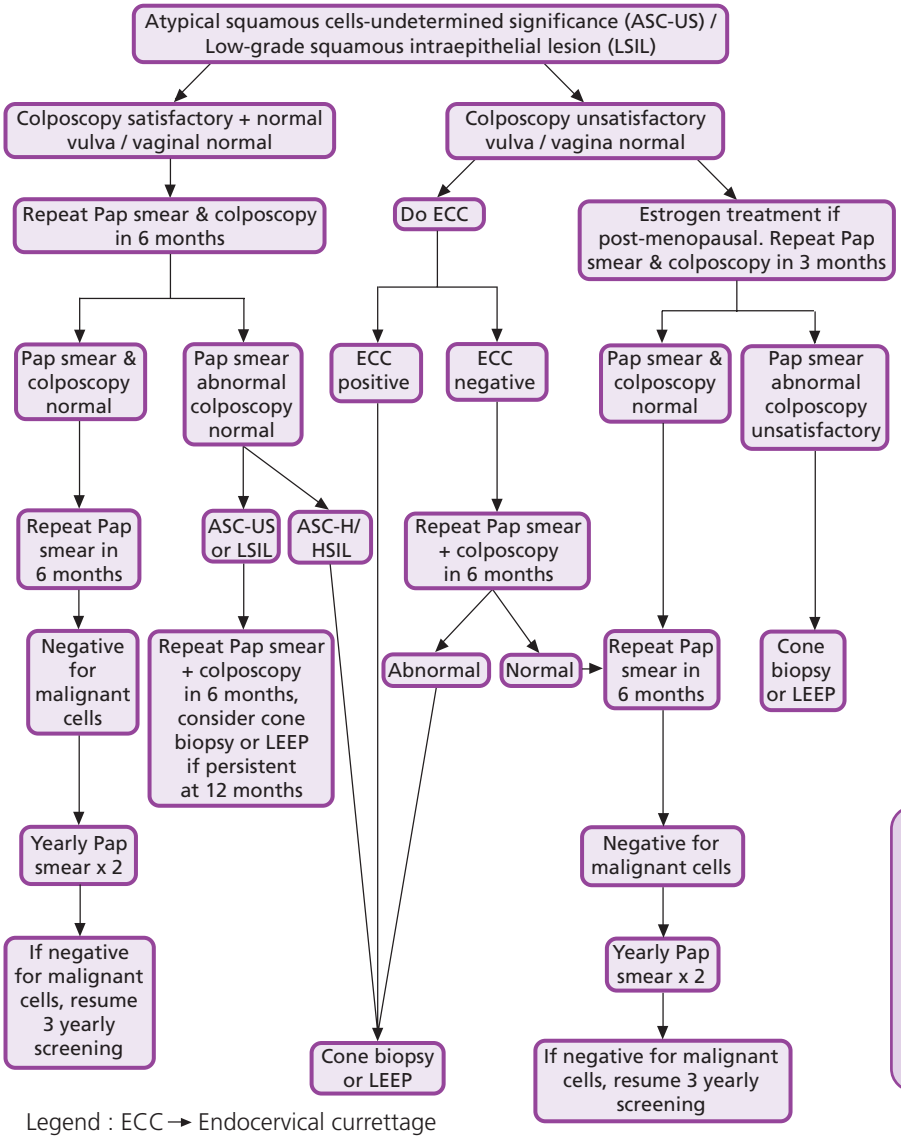
* Refer to criteria for ablation in 7.3

8 SPECIAL SITUATIONS

Note:

Management should be individualised.
Consider expert opinion including pathology review.

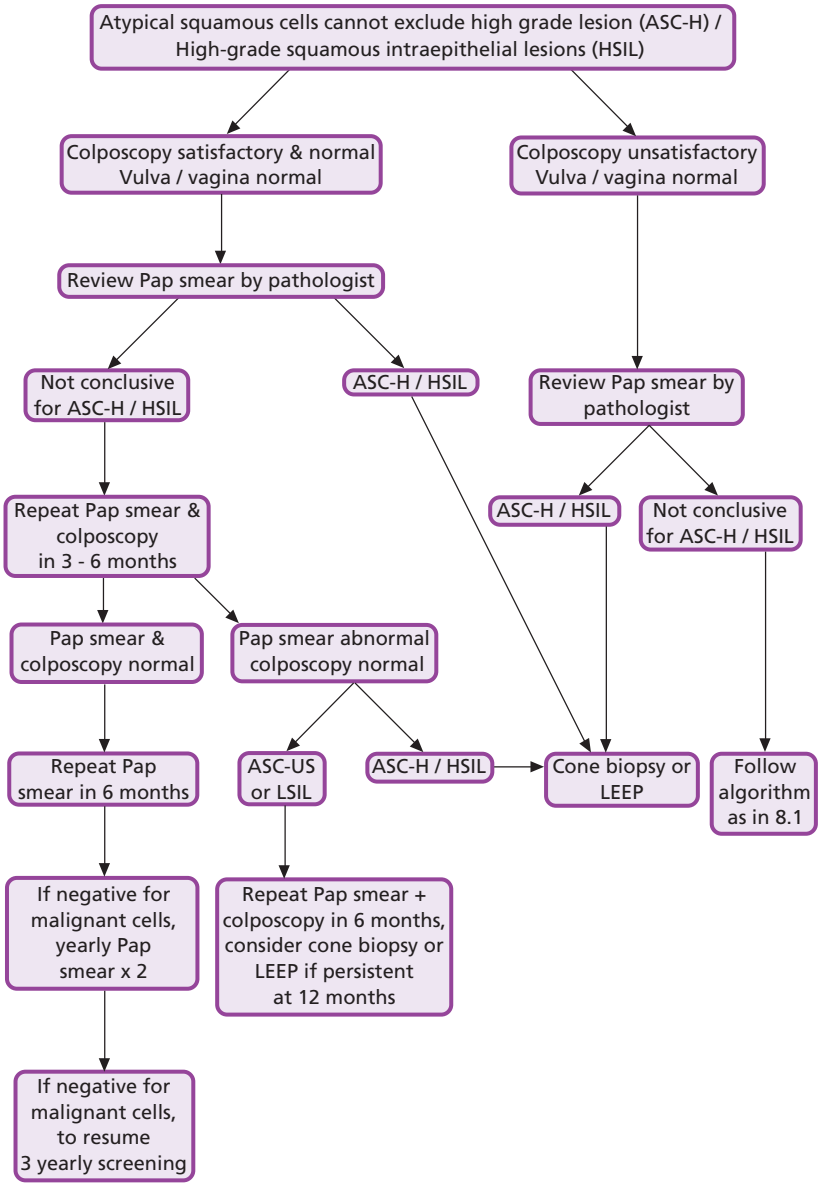
8.1 Abnormal Smear (ASC-US / LSIL) & Unsatisfactory or Normal Colposcopy



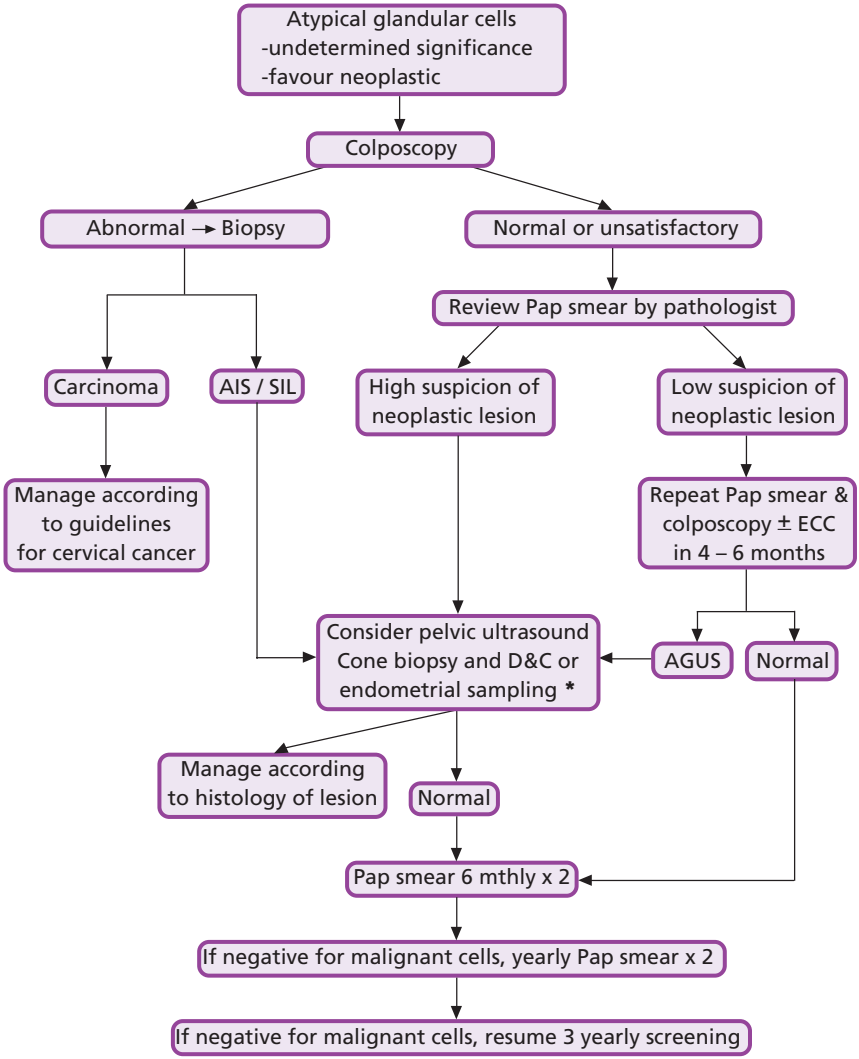
Legend : ECC → Endocervical currettage

Note : Management should be individualised. Consider expert opinion including pathology review.

8.2 Abnormal Smear (ASC-H / HSIL) & Unsatisfactory or Normal Colposcopy



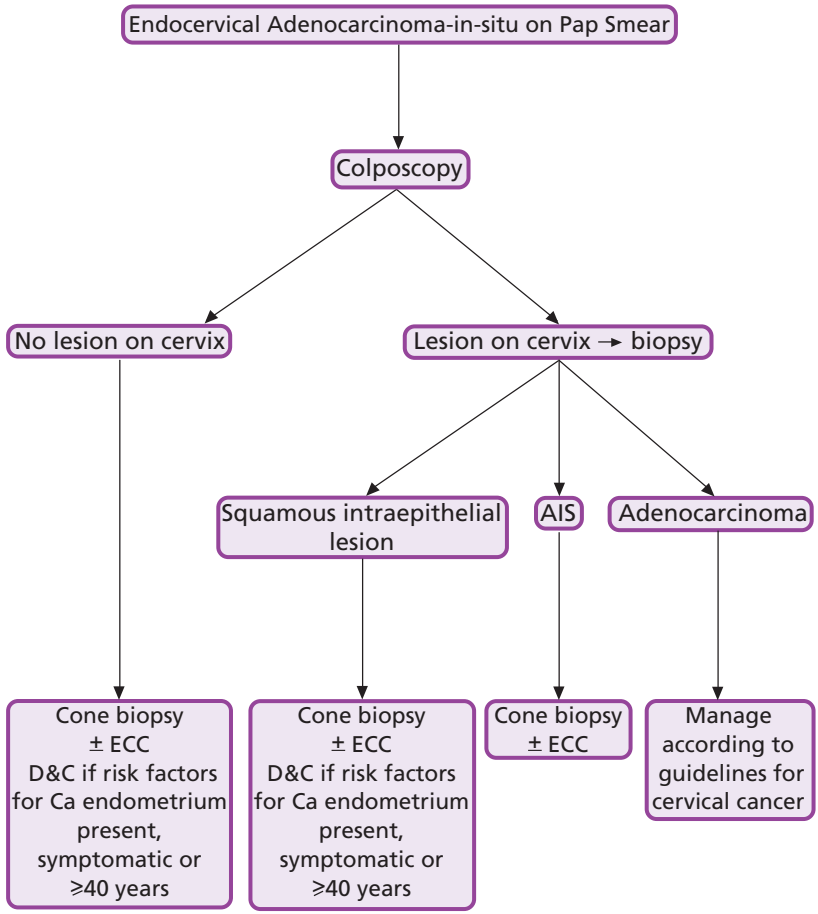
8.3 Atypical Glandular Cells



* If risk factors for Ca endometrium are present, or the patient is symptomatic or ⩾ 40 years → D&C (± hysteroscopy) is advised for endometrial tissue evaluation

Note : If histology of cone biopsy and D&C normal → to investigate for disease in ovary, fallopian tubes and peritoneum.

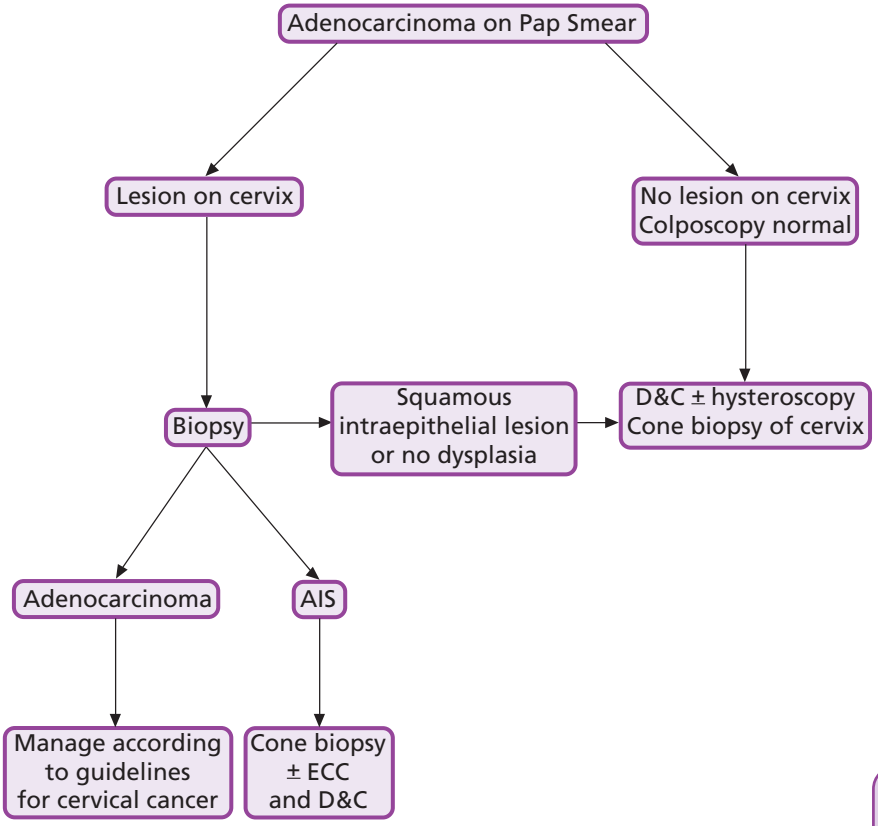
8.4 Endocervical Adenocarcinoma-in-situ on Pap Smear



Legend: ECC → Endocervical currettage

Note : If histology of cone biopsy and D&C normal → to investigate for disease in ovary, fallopian tubes and peritoneum.

8.5 Adenocarcinoma on Pap Smear



Note : If histology of D&C and cone biopsy normal → to investigate for disease in ovary, fallopian tubes and peritoneum.

REFERENCES

1. Duncan ID (ed). Guidelines for clinical practice and programme management 2nd edition. National Health Service Cervical Screening Programme Publication No. 8 1997.

2. Screening to prevent cervical cancer: Guidelines for the management of women with screen detected abnormalities. Report by the National Health and Medical Research Council for the Organised Approach to preventing cancer of the cervix. Australian Government Publishing Service, Canberra 1994.

3. IARC Working Group on Evaluation of Cervical Cancer Screening Programmes. "Screening for squamous cervical cancer: Duration of low risk after negative results of cervical cytology and its implication for screening policies." Br Med J 1986; 293: 659-64.

4. From the Centres for Disease Control and Prevention. Incidence of Pap test abnormalities within 3 years of a normal Pap test - United States, 1991 - 1998. JAMA 2000; 284 (21): 2714-5.

5. Gram IT, Macaluso M, Stalsberg H. Incidence of cervical intraepithelial neoplasia grade III, and cancer of the cervix uteri following a negative Pap smear in an opportunistic screening. Acta Obstet Gynecol Scand 1998; 77 (2): 228-32.

6. Mitchell MF, Schottenfeld D, Tortolero-Luna G, Cantor SB, Richards-Kortum R. Colposcopy for the diagnosis of squamous intraepithelial lesions: A meta-analysis. Obstet Gynecol 1998; 91 (4): 626-31.

7. M I Shafi, DM Luesley, JA Jordan, JA Dunn, TP Rollason, M Yates. Randomised trial of immediate versus deferred treatment strategies for the management of minor cervical cytological abnormalities. British Journal of O&G 1997; 104: 590-4.

8. Flannelly G, Kitchener H. Every woman with an abnormal cervical smear should be referred for treatment: debate. Clin Obstet Gynecol 1995; 38 (3): 585-91.

9. Manetta A, Keefe K, Lin F, Ahdoot D, Kaleb V. Atypical glandular cells of undetermined significance in cervical cytologic findings. Am J Obstet Gynecol 1999; 180 (4): 883-8.

10. Kim TJ, Kim HS, Park CT, Park IS, Hong SR, Park JS, Shim JU. Clinical evaluation of follow-up methods and results of atypical glandular cells of undetermined significance (AGUS) detected on cervicovaginal Pap smears. Gynecol Oncol 1999; 73 (2): 292-8.

11. McIndoe WA, McLean MR, Jones RW, Mullins PR. The invasive potential of carcinoma in situ of the cervix. Obstet Gynecol 1984; 64 (4) : 451-8.

12. Cox JT. Management of cervical intraepithelial neoplasia. Lancet 1999; 353 (9156): 857-9.

13. Shafi MI, Luesley DM. Management of low grade lesions: Follow-up or treat? Ballieres Clin Obstet Gynaecol 1995; 9 (1): 121-31.

14. G Flannelly, D Anderson, HC Kitchener, E M F Mann, M Campbell, P Fisher, F Walker. Management of women with mild and moderate cervical dyskaryosis. BMJ; 308: 1399-403.

15. Martin-Hirsch PL, Paraskevaidis E, Kitchener H. Surgery for cervical intraepithelial neoplasia. Cochrane Database Syst Rev 2, CD001318, 2000.

16. Duggan BD, Felix JC, Muderspach LI, Gebhardt JA, Groshen S, Morrow CP, Roman LD. Cold-knife conization versus conization by the loop electrosurgical excision procedure: a randomized, prospective study. Am J Obstet Gynecol 1999; 180 (2 Pt 1): 276-82.

17. Narducci F, Occelli B, Boman F, Vinatier D, Leroy JL. Positive margins after conization and risk of persistent lesion. Gynecol Oncol 2000; 76 (3): 311-4.

18. Dobbs SP, Asmussen T, Nunns D, Hollingworth J, Brown LJ, Ireland D. Does histological incomplete excision of cervical intraepithelial neoplasia following large loop excision of transformation zone increase recurrence rates? A six year cytological follow up. Br J Obstet Gynaecol 2000; 107 (10) : 1298-301.

19. K Mohamed-Noor, MA Quinn, J Tan. Outcomes after cervical cold knife conization with complete and incomplete excision of abnormal epithelium: A review of 699 cases. Gynecologic Oncology 1997; 67: 34-8.

20. Grainne Flannelly, Heather Langhan, Lata Jandial, Evelyn Mann, Marion Campbell, Henry Kitchener. A study of treatment failures following large loop excision of the transformation zone for the treatment of cervical intraepithelial neoplasia. British Journal of O&G 1997; 104: 718-22.

21. ES Andersen, B Pedersen, K Nielsen. Laser conization : The results of treatment of cervical intraepithelial neoplasia. Gynecologic Oncology 1994; 54: 201-4.

22. WP Soutter, A de Barros Lopes, Astrid Fletcher, JM Monaghan, ID Duncan, E Paraskevaidis, HC Kitchener. Invasive cervical cancer after conservative therapy for cervical intraepithelial neoplasia. Lancet 1997; 349: 978-80.

23. Shin CH, Schorge JO, Lee KR Sheets EE. Conservative management of adenocarcinoma in situ of the cervix. Gynecol Oncol 2000; 79 (1): 6-10.

24. Ostor AG, Duncan A, Quinn M, Rome R. Adenocarcinoma-in-situ of the uterine cervix : An experience with 100 cases. Gynecol Oncol 2000; 79 (2): 207-10.

25. Palle C, Bangsboll S, Andreasson B. Cervical intraepithelial neoplasia in pregnancy. Acta Obstet Gynecol Scand 2000; 79 (4): 306-10.

26. Woodrow N, Permezel M, Butterfield L, Rome R, Tan J, Quinn M. Abnormal cervical cytology in pregnancy: Experience of 811 cases. Aust N Z J Obstet Gynaecol 1998; 38 (2) : 161-5.

27. Milne DS, Wadehra V, Mennim D, Wagstaff TI. A prospective follow up study of women with colposcopically unconfirmed positive cervical smears. Br J Obstet Gynaecol 1999; 106 (1) : 38-41.

28. Roche DH, Spicer N. The clinical significance of atypical squamous cells of undetermined significance: A laboratory audit of cervical reporting. N Z Med J 2001 23; 114 (1126) : 64-6.

29. Lambert B, Boivin Y, Lepage Y. Atypical squamous cells of undetermined significance (ASC-US): clinical-cytological significance. Int J Gynecol Cancer 1999; 9 (4): 329-32.

30. Law KS, Chang TC, Hsueh S, Jung SM, Tseng CJ, Lai CH. High prevalence of high grade squamous intraepithelial lesions and microinvasive carcinoma in women with a cytologic diagnosis of low grade squamous intraepithelial lesions. J Reprod Med 2001; 46 (1): 61-4.

ACKNOWLEDGEMENTS

Workgroup Members

Chairperson

Clinical Assoc Prof Ho Tew Hong

Members

Dr Chew Sung Hock	KK Women's & Children's Hospital
Assoc Prof A Ilancheran	Academy of Medicine, Singapore
Dr Lee I Wuen	Raffles Hospital
Assoc Prof Lim Fang Kan	National University Hospital
Dr Lim-Tan Soo Kim	Singapore General Hospital
Dr Jeffrey Low	KK Women's & Children's Hospital
Dr Quek Swee Chong	KK Women's & Children's Hospital
Dr Pritam Singh	Society for Colposcopy & Cervical Pathology of Singapore
Dr Tay Eng Hseon	Obstetrical & Gynaecological Society of Singapore
Clinical Assoc Prof Tay Sun Kuie	Singapore General Hospital
Assoc Prof Tham Kok Fun	National University Hospital

3 Second Hospital Avenue, Singapore 168937
www.hpb.gov.sg / www.healthylife.org.sg

Designed & printed by Grace Communications Pte Ltd