FOGSI GCPR

SCREENING AND MANAGEMENT OF PREINVASIVE LESIONS OF CERVIX AND HPV VACCINATION

FOGSI GYNAECOLOGIC ONCOLOGY COMMITTEE

January, 2018

Introduction

DR NEERJA BHATLA
Chairperson
FOGSI Gynaecologic Oncology Committee

India is a land of diversity and this is reflected also in the varied practices followed for cervical screening. For years we have followed guidelines of various foreign societies, simultaneously lamenting the lack of uniformity of resources in our country. Also, each one of us works across different scenarios, sometimes in a tertiary hospital with state of the art facilities and sometimes in a camp setting. The FOGSI Gynaecologic Oncology Committee takes great pleasure in presenting GCPR for the Indian situation. The first step is to identify which situation you are working in – good resource or low resource – and accordingly to identify the options for screening, triage for confirmation of diagnosis and management. Recognising that the bulk of cervical cancer in India manifests after the age of 30 years, FOGSI recommends that screening should be started at 25 years for good resource and 30 years for low resource settings. FOGSI recognises that while HPV testing is the best method, all the screening tests, namely, HPV, cytology, Co-testing with both HPV and cytology, and VIA, are all valid options. The critical steps are maintenance of quality control and follow-up and treatment of screen detected lesions. Single visit approach is to be practiced wherever possible to minimise non-compliance and loss to follow-up. The charts show the screening algorithms for each type of screening method and management of various grades of CIN. All options have been evaluated and recommended based on global evidence and Indian data which have been extensively reviewed by the group of experts.

Primary prevention with HPV vaccine is strongly recommended. FOGSI endorses the WHO recommendation that the preferred age group is under 15 years, where two doses can be administered at an interval of 6 months. The charts also outline the recommendations for older girls and women and also for special situations. It is to be emphasised that screening must be continued in all vaccinated women too.

This work would not have been possible without the inspiration from our seniors and the hard work and commitment of the expert panel. I am grateful to each one of them for their untiring support and insights, guided by personal experience. I am also thankful to PSI for their partnership and support to bring this work to fruition. I am confident that you will find the FOGSI GCPR useful in your day-to-day practice and helpful in our common battle to eliminate cervical cancer.

January 17, 2018

FOGSI Good Clinical Practice Recommendation

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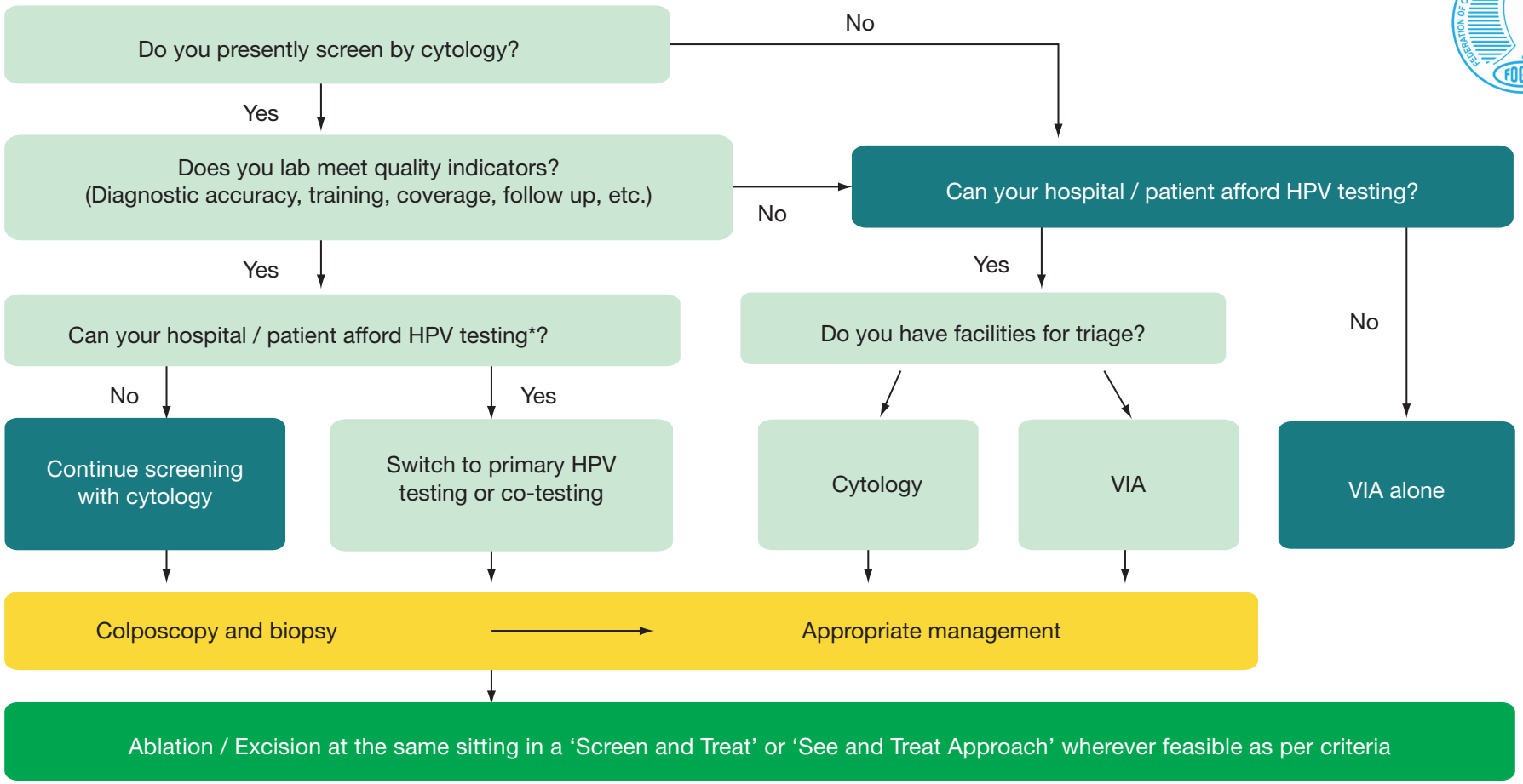
SCREENING AND TREATMENT OF PREINVASIVE LESIONS OF CERVIX

FOGSI GCPR on
"Choosing the most appropriate screening test for your practice"



Adapted from WHO guidelines for Screening and treatment of Precancerous lesions for cervical cancer prevention.

Criteria of various single visit approach strategies

See and Treat

- In Colposcopy Clinics
- Patient referred with abnormal cytology report
- Colposcopy scoring indicates a high grade lesion
- Simultaneous treatment done – excision or ablation
- Low probability of over-treatment because of high specificity of cytology
- Post-hoc analysis of biopsy report/excision specimen

Screen and Treat

- In Public Health Programs
- VIA detects abnormal lesion
- Criteria for ablation fulfilled
- Treat immediately, with or without biopsy
- Lower probability of over-treatment in high prevalence areas
- Post-hoc analysis is possible if biopsy was taken

Resource-based strategies for cervical cancer screening and management of CIN

SETTING	SCREENING TOOLS	TRIAGE TOOLS	MANAGEMENT OPTIONS	SINGLE VISIT APPROACH
Good resource settings	Primary HPV test *or* Co-testing (HPV test + Cytology) *or* Cytology *or* VIA	Cytology ± newer modalities* HPV test HPV Genotyping-16/18 Colposcopy and biopsy VIA and biopsy	LEEP Conization Cryotherapy Thermo-coagulation	See and Treat approach
Limited resource settings**	VIA	Colposcopy, if available Biopsy	Cryotherapy LEEP Conization ± Thermo-coagulation	Screen and Treat *or* Screen, See and Treat approach

* Newer modalities (p16, Ki 67 testing, mRNA testing, E6,E7 protein testing).

** Affordable HPV test (if available), including self-sampling, can be used.

Resource-based cervical cancer screening recommendation

	GOOD RESOURCE SETTINGS	LIMITED RESOURCE SETTINGS
Modalities	HPV testing • Primary HPV testing • Co-testing (HPV & cytology) Cytology Colposcopy and biopsy VIA	VIA Colposcopy ± Biopsy
Target Age Group (years)	25 - 65	30 - 65 (N.B.: In postmenopausal women, screening with VIA may not be as effective)
Age to start (years)	Cytology at 25 Primary HPV Testing / Co-testing at 30	VIA at 30
Frequency	Primary HPV Testing *or* Co-testing – every 5 years Cytology – every 3 years	Every 5 years (at least 1-3 times in a lifetime)

Resource-based cervical cancer screening recommendation

	GOOD RESOURCE SETTINGS	LIMITED RESOURCE SETTINGS
Age to stop (years)	• 65 with consistent negative results in last 15 years • Women with no prior screening should undergo tests once at 65 years and, if negative, they should exit screening.	
Follow-up method after treatment; interval	HPV testing (preferred) *or* cytology 12 months	VIA 12 months
Screening following abnormal reports ≥ CIN 2+, irrespective of method of treatment	20 years	
Screening in hysterectomized women	• Following hysterectomy in which cervix was removed for benign causes : no need for screening, unless there is history of previous cervical intra-epithelial neoplasia • Absence of cervix must be confirmed by clinical records or examination • If indications for hysterectomy unclear, screening may be performed at clinician's discretion	
Follow up in women with CIN in hysterectomy HPE report	Need to be screened with HPV at 6 months and 18 months	

The Bethesda system for reporting Pap smear

Epithelial cell abnormalities

ABBREVIATION	TERMINOLOGY
NILM	Negative for Intra-epithelial Lesion or Malignancy
ASCUS	Atypical Squamous Cells of Undetermined Significance
ASC-H	Atypical Squamous Cells: cannot exclude High grade Squamous Intra-epithelial Lesion
LSIL	Low-grade Squamous Intra-epithelial Lesion
HSIL	High grade Squamous Intra-epithelial Lesion
SCC	Squamous Cell Carcinoma

Glandular cell abnormalities

ABBREVIATION	TERMINOLOGY
AGC	Atypical glandular cells (specify endocervical, endometrial or NOS, i.e., Not Otherwise Significant)
AGC-FN	Atypical Glandular Cells – Favor Neoplastic
AIS	Endocervical Adenocarcinoma in Situ
	Endometrial cells in a woman > 40 years of age
	Adenocarcinoma
	Others

List of other Abbreviations

HPV : Human Papillomavirus
VIA : Visual Inspection with Acetic Acid
CIN : Cervical Intraepithelial Neoplasia
LEEP : Loop Electrosurgical Excision Procedure
TZ : Transformation Zone

Index – FOGSI Recommendation for
Cervical Cancer Screening using HPV testing/Cytology/VIA

Index – FOGSI GCPR Recommendation for Management of Biopsy Proven Cervical Intraepithelial Neoplasia (CIN)

Chart 1

Screening of women aged > 30 years with Primary HPV testing

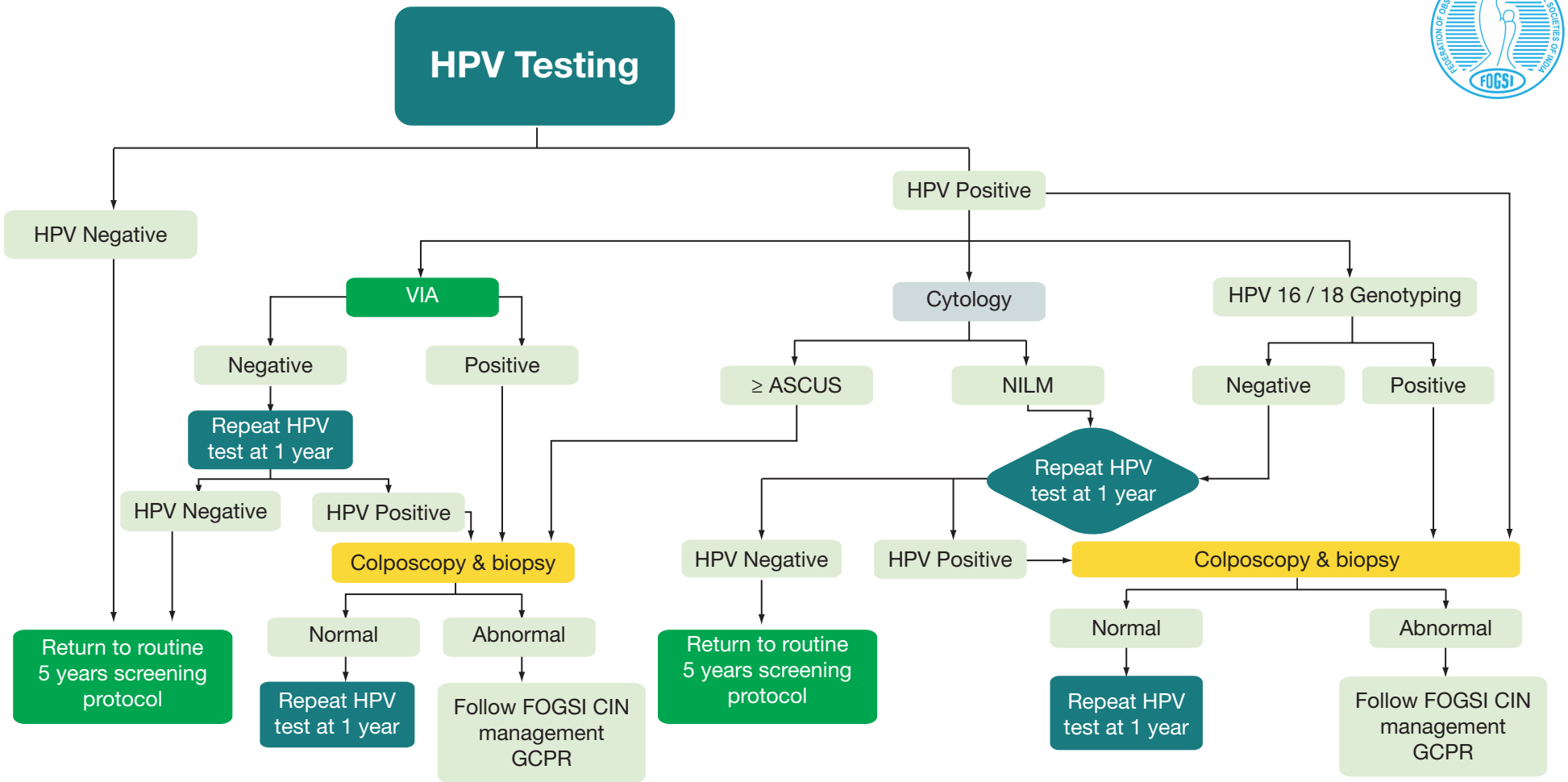


Chart 2

Screening with Co-testing (HPV test with cytology) in women aged > 30 years

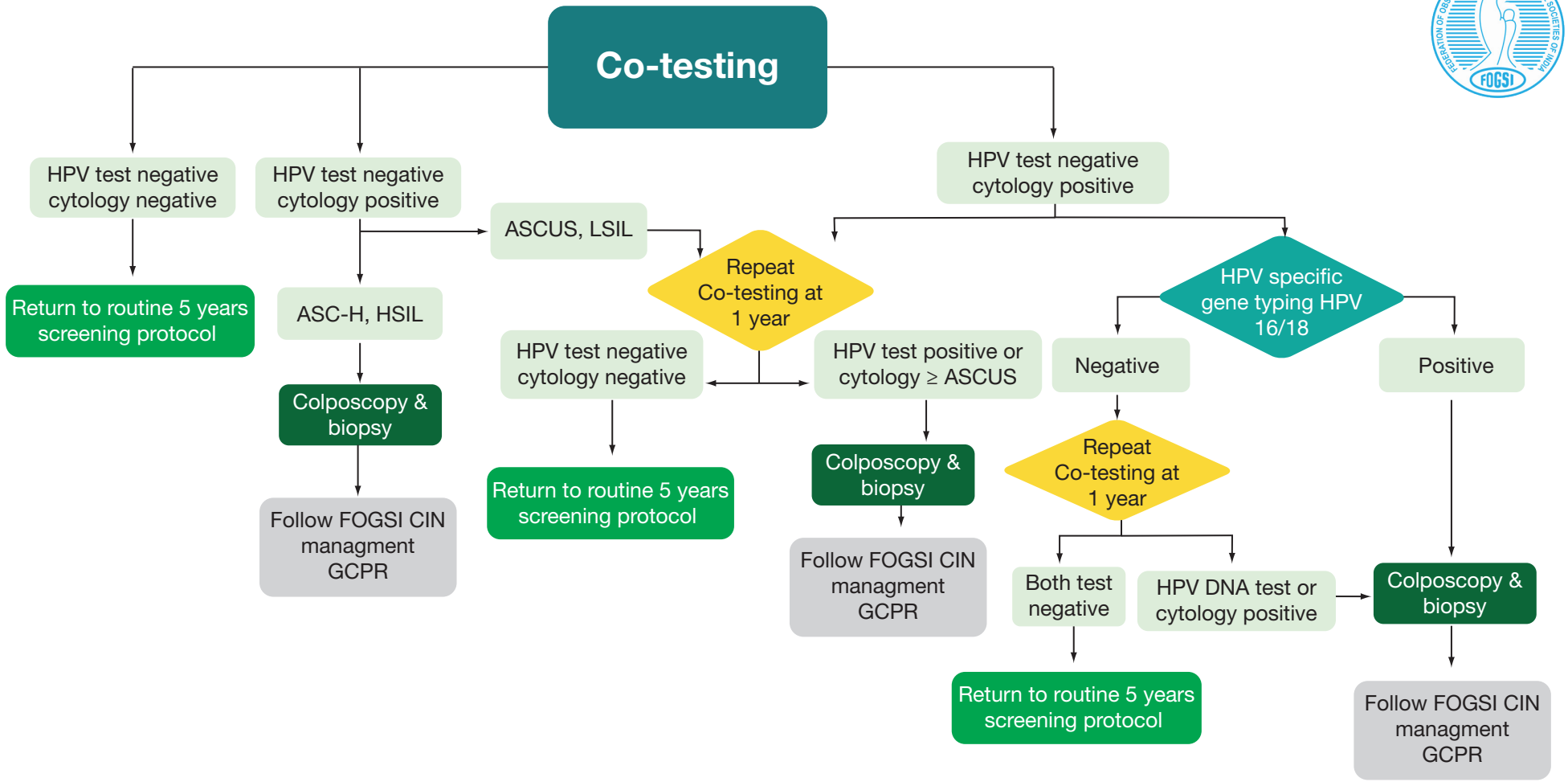


Chart 3

Management of ASCUS in women aged 30-64 years

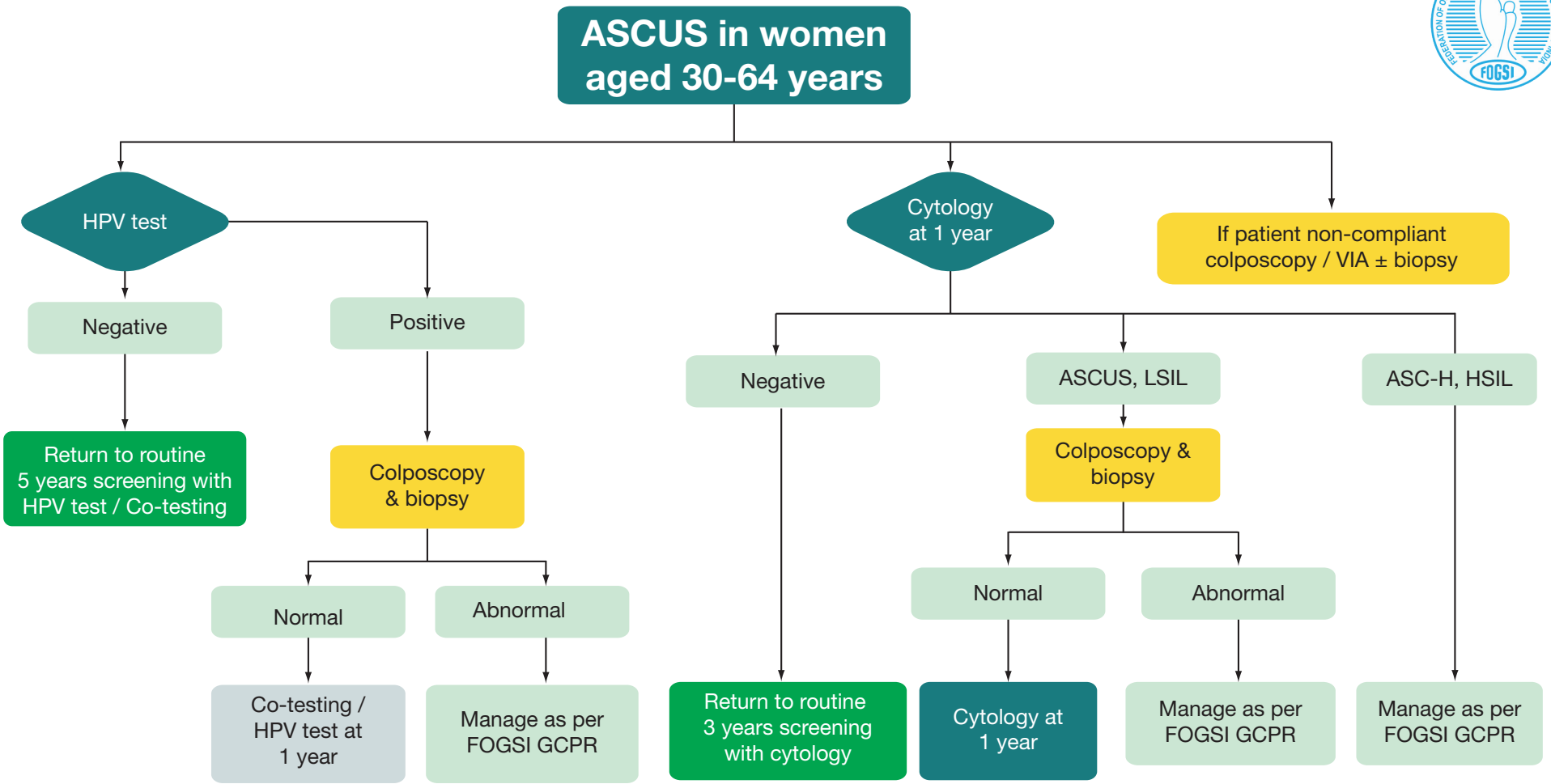


Chart 4

SCREENING WITH CYTOLOGY – MANAGEMENT OF ABNORMAL PAP SMEAR

Management of LSIL in women aged 30-64 years

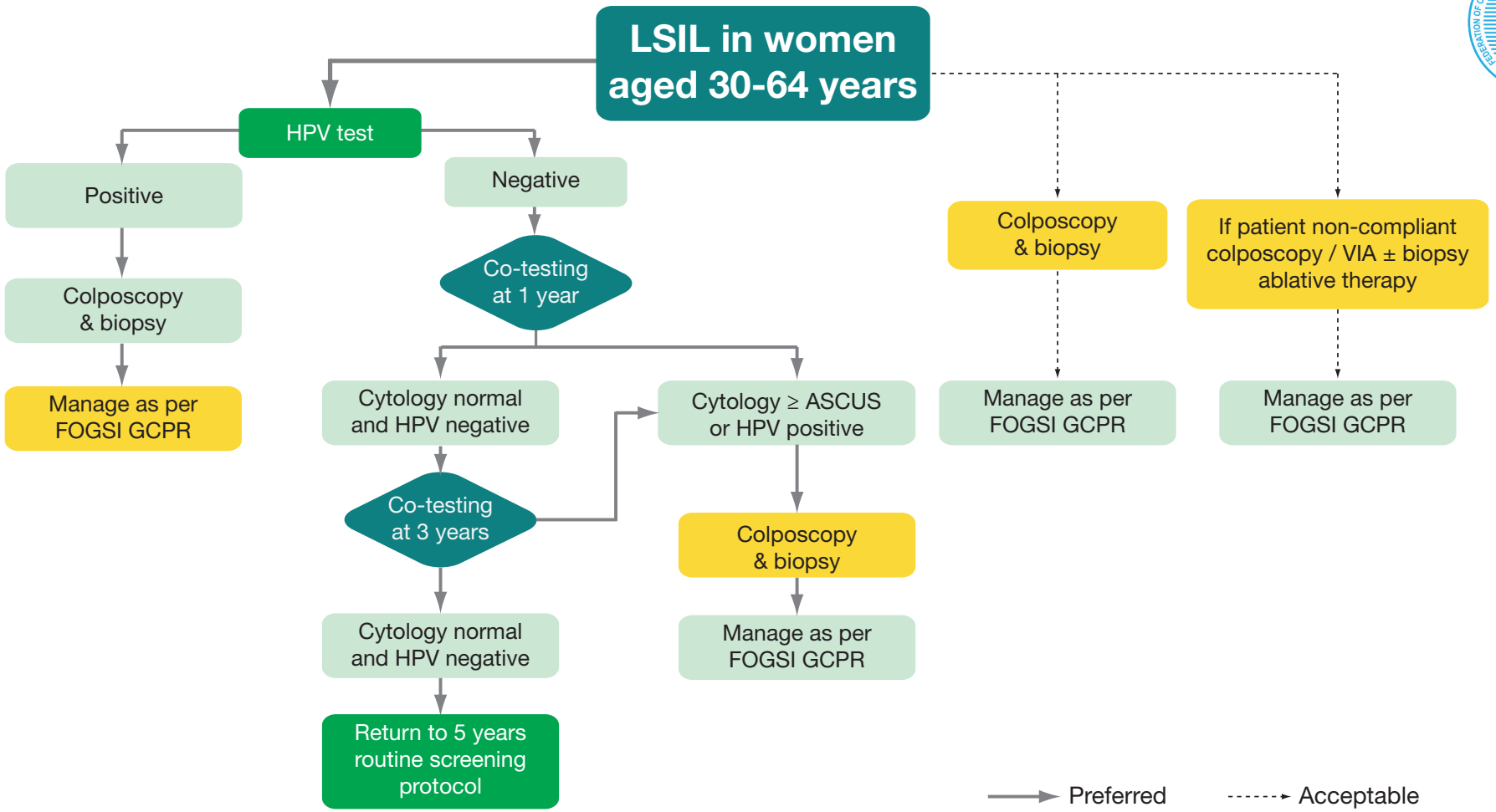


Chart 5

Management of LSIL in women aged 25-29 years

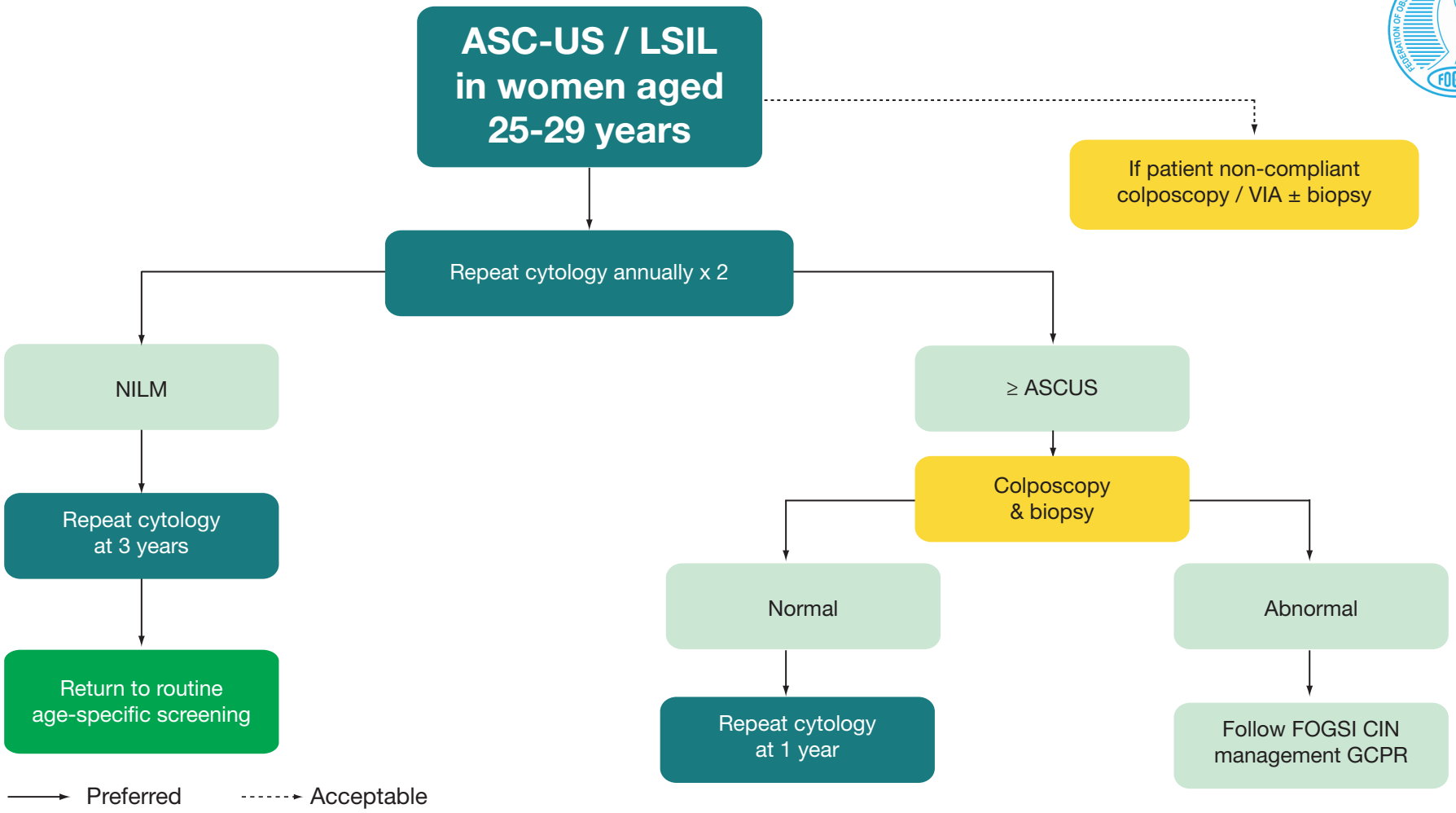
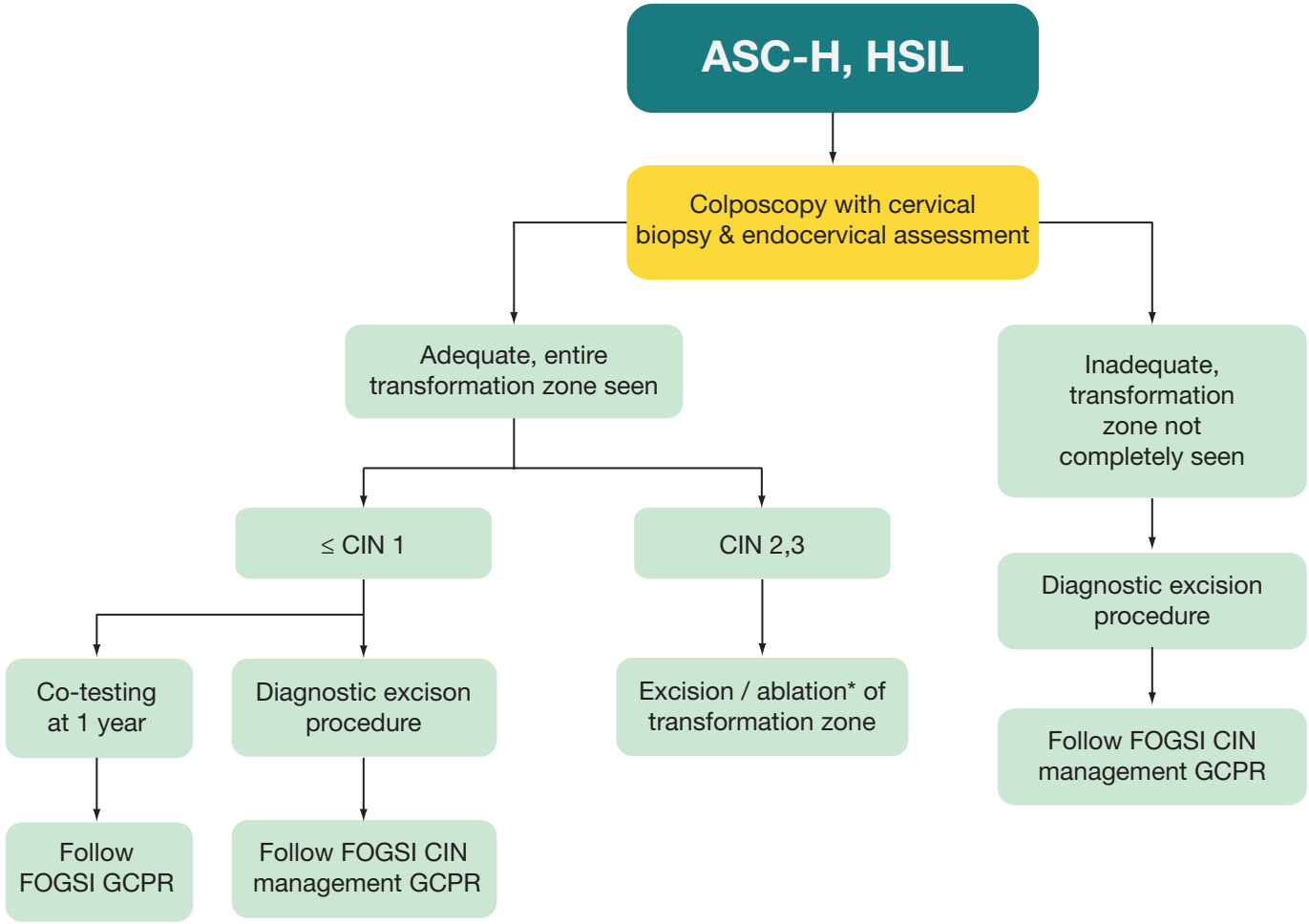


Chart 6

SCREENING WITH CYTOLOGY – MANAGEMENT OF ABNORMAL PAP SMEAR

Management of ASC-H, HSIL in women aged ≥ 30 years



***Eligibility for Ablative procedures**

1. Lesion should be entirely visible and occupy not more than two quadrants of cervix
2. Entire lesion should be located on ectocervix without any vaginal and / or endocervical extension
3. Lesion can be adequately covered by largest cryotherapy probe available
4. There is no suspicion of invasive cancer
5. Screen and treat by cryotherapy is contraindicated in cases of postcoital or postmenopausal bleeding, obvious cervical growth, imegular surface or bleeds on touch

Chart 7

Management of ASC-H, HSIL in women aged < 30 years and desirous of pregnancy

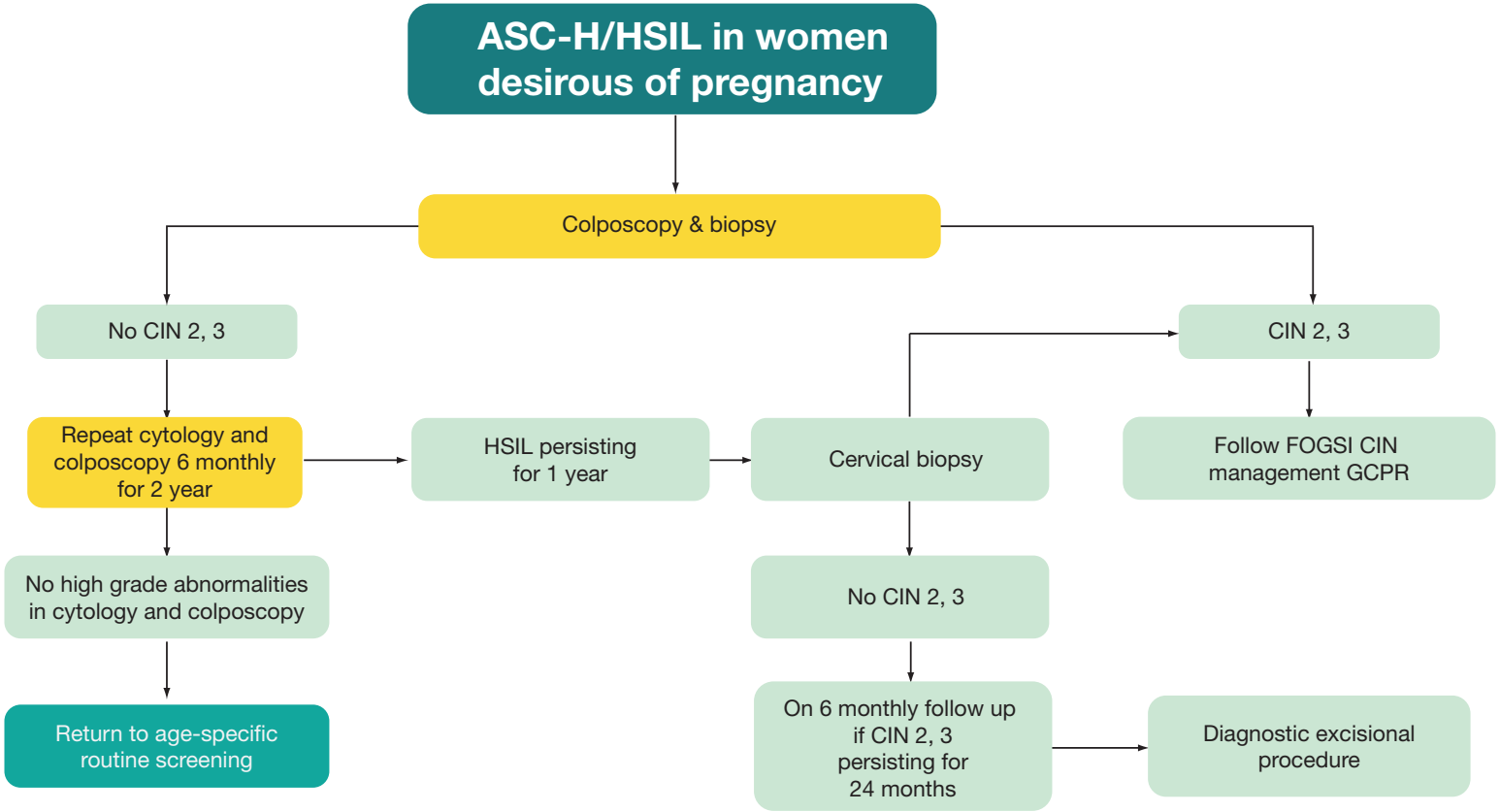


Chart 8

SCREENING WITH CYTOLOGY – MANAGEMENT OF ABNORMAL PAP SMEAR

Management of abnormal glandular cells:
Atypical Endometrial Cells

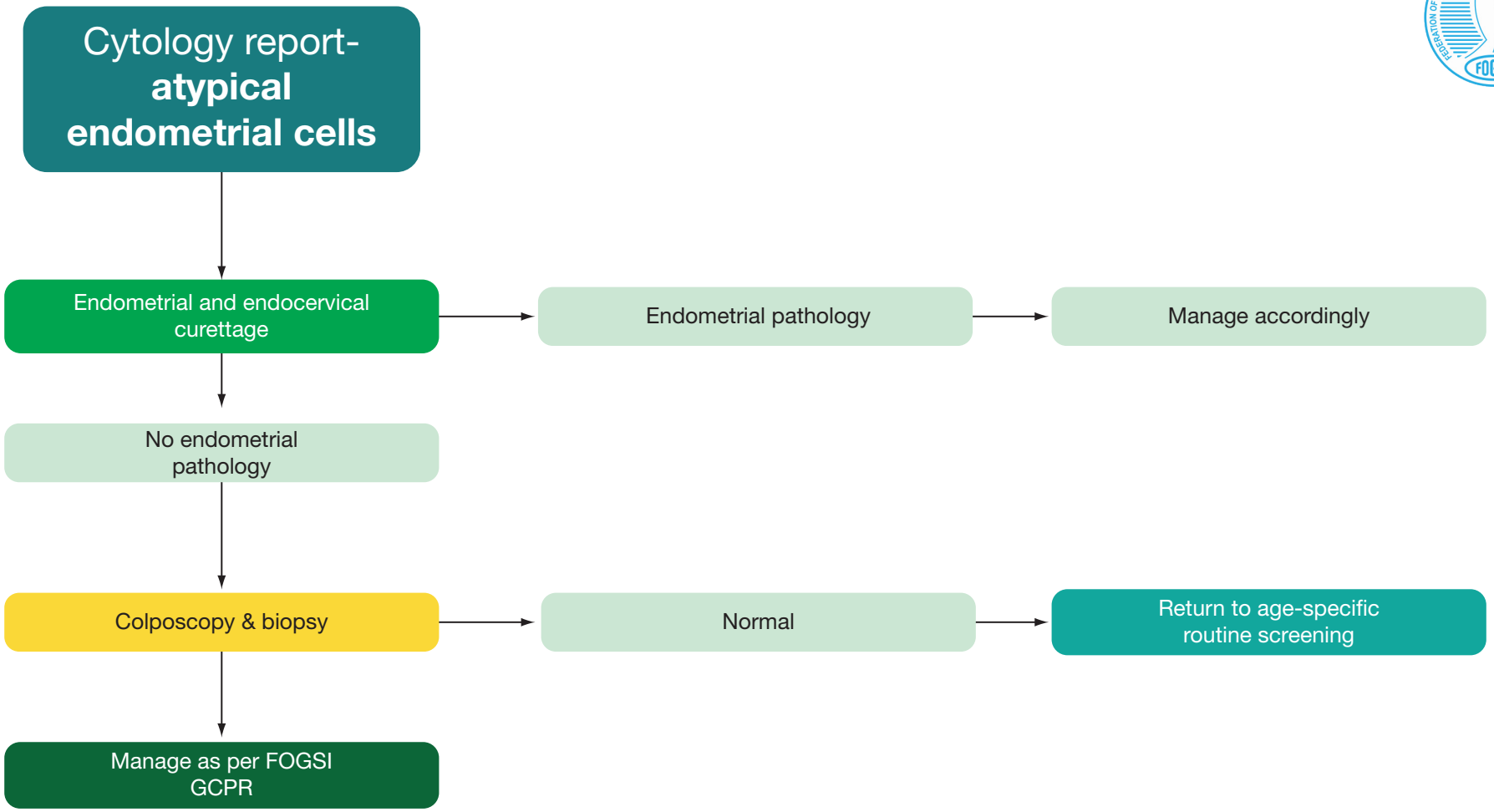
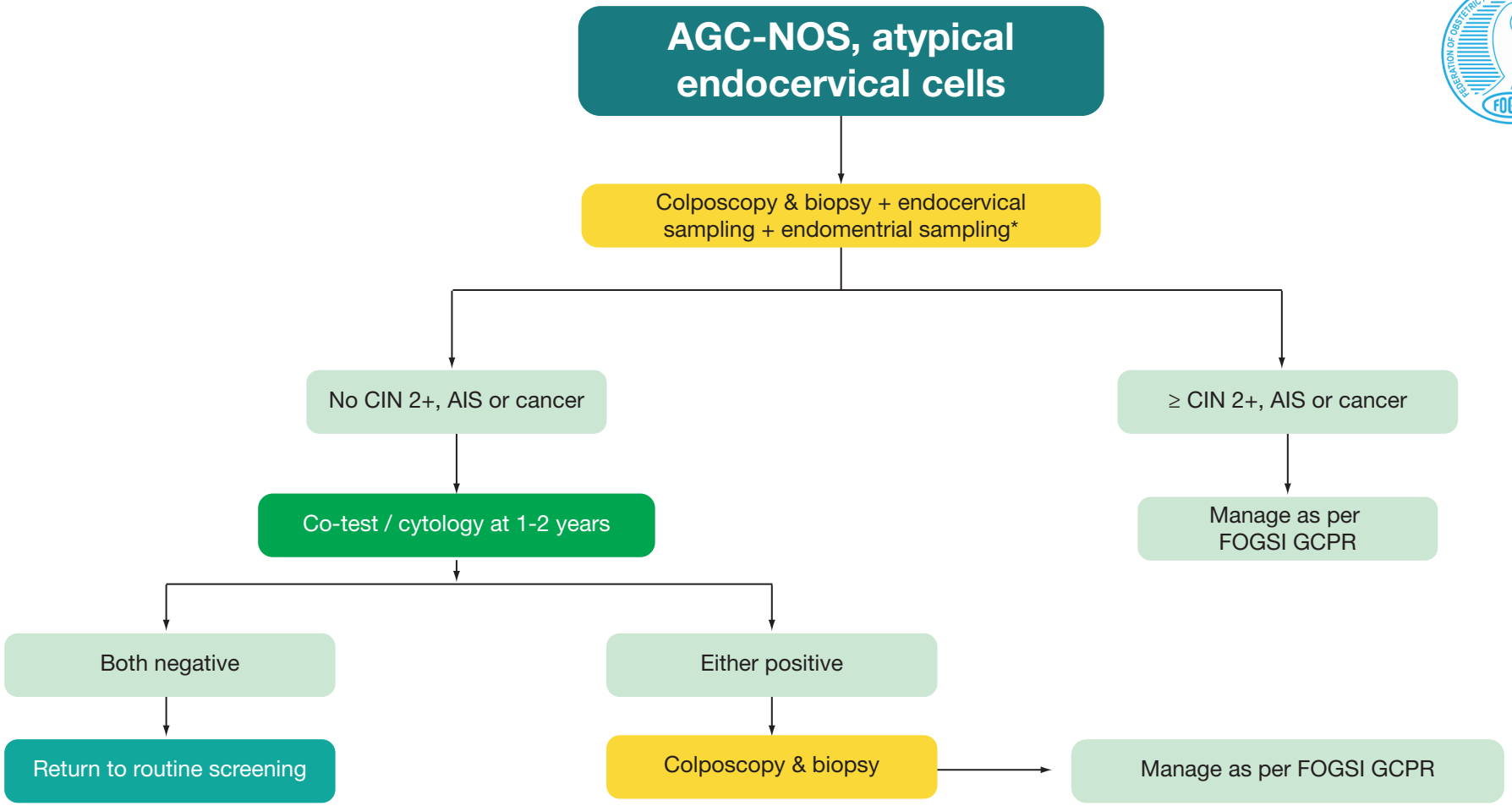


Chart 9

Management of abnormal glandular cells:
AGC-NOS, Atypical Endocervical Cells

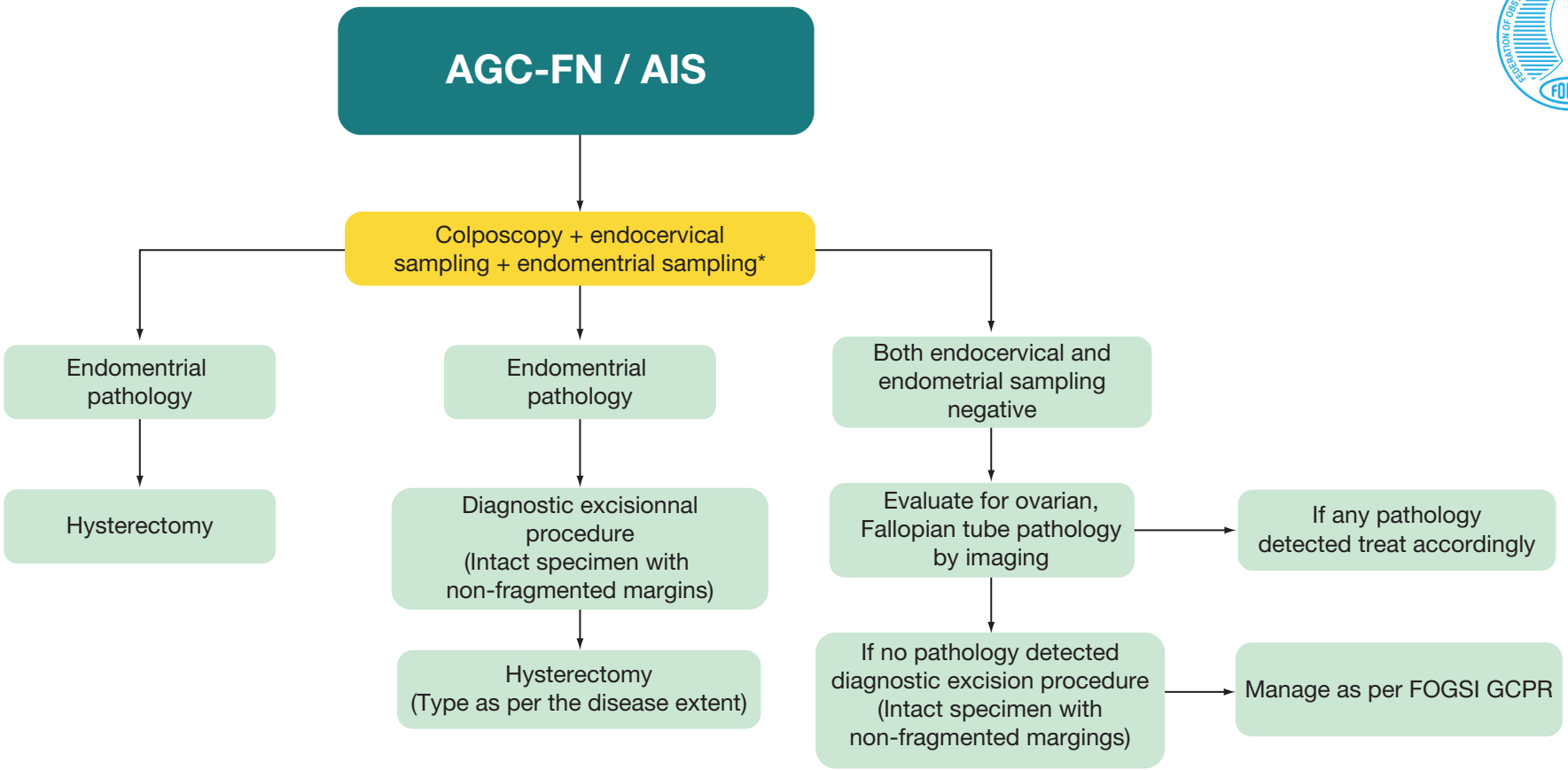


AGC-NOS: Atypical Glandular Cells – Not Otherwise Specified

Chart 10

SCREENING WITH CYTOLOGY – MANAGEMENT OF ABNORMAL PAP SMEAR

Management of abnormal glandular cells: AGC-FN / AIS



*Age > 35 yrs, high risk factors, e.g., obesity, chronic anovulation

AGC-FN - Atypical Glandular Cells Favouring Neoplasia; AIS - Adenocarcinoma in Situ

Chart 11

Screening with VIA

*** Eligibility for Ablative Procedures**

1. Lesion should be entirely visible and occupy not more than two quadrants of cervix
2. Entire lesion should be located on ectocervix without any vaginal and/or endocervical extension
3. Lesion can be adequately covered by largest cryotherapy probe available
4. There is no suspicion of invasive cancer
5. Screen and treat by cryotherapy is contraindicated in cases of postcoital or postmenopausal bleeding, obvious cervical growth, imegular surface or bleeds on touch

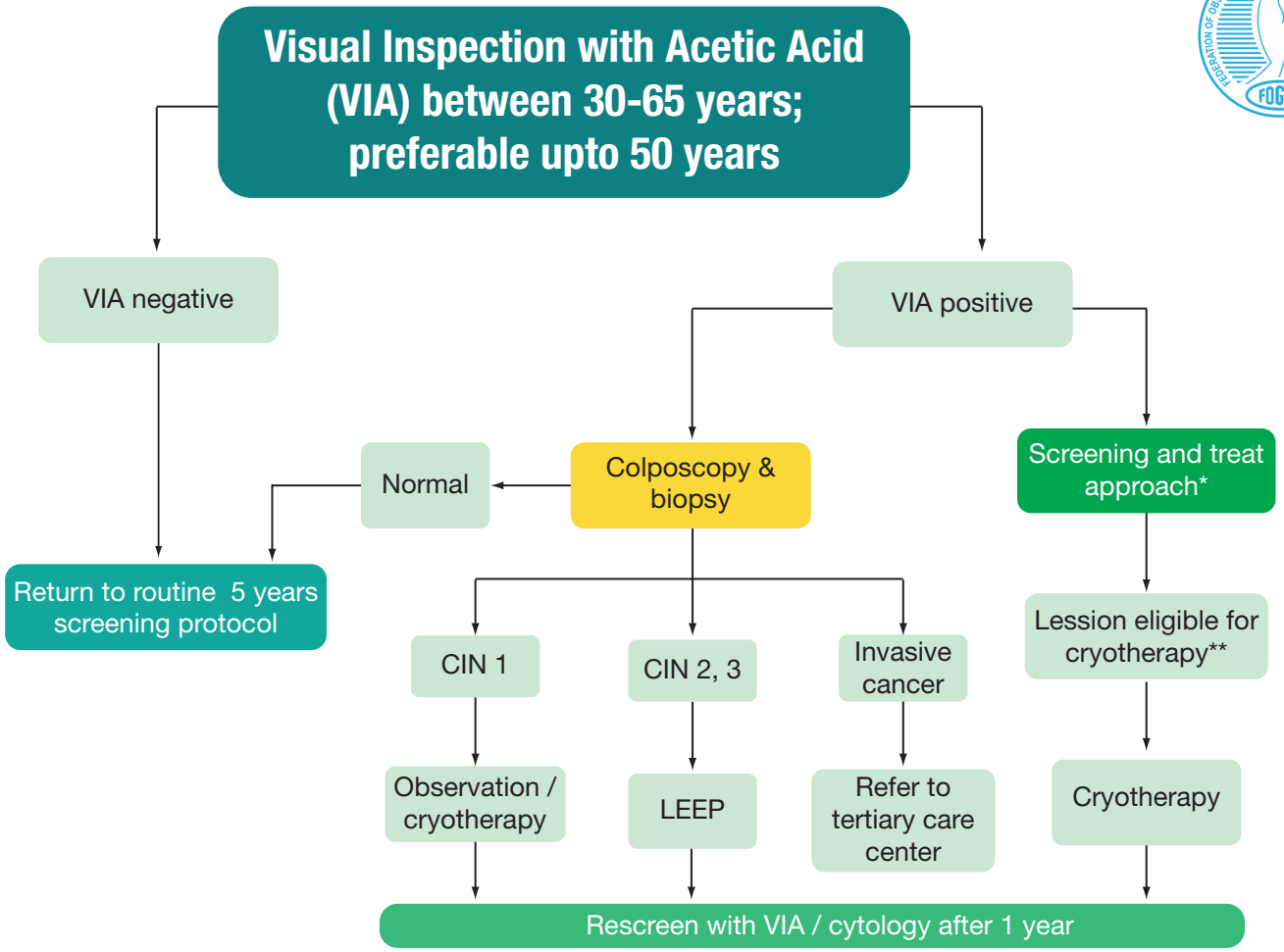
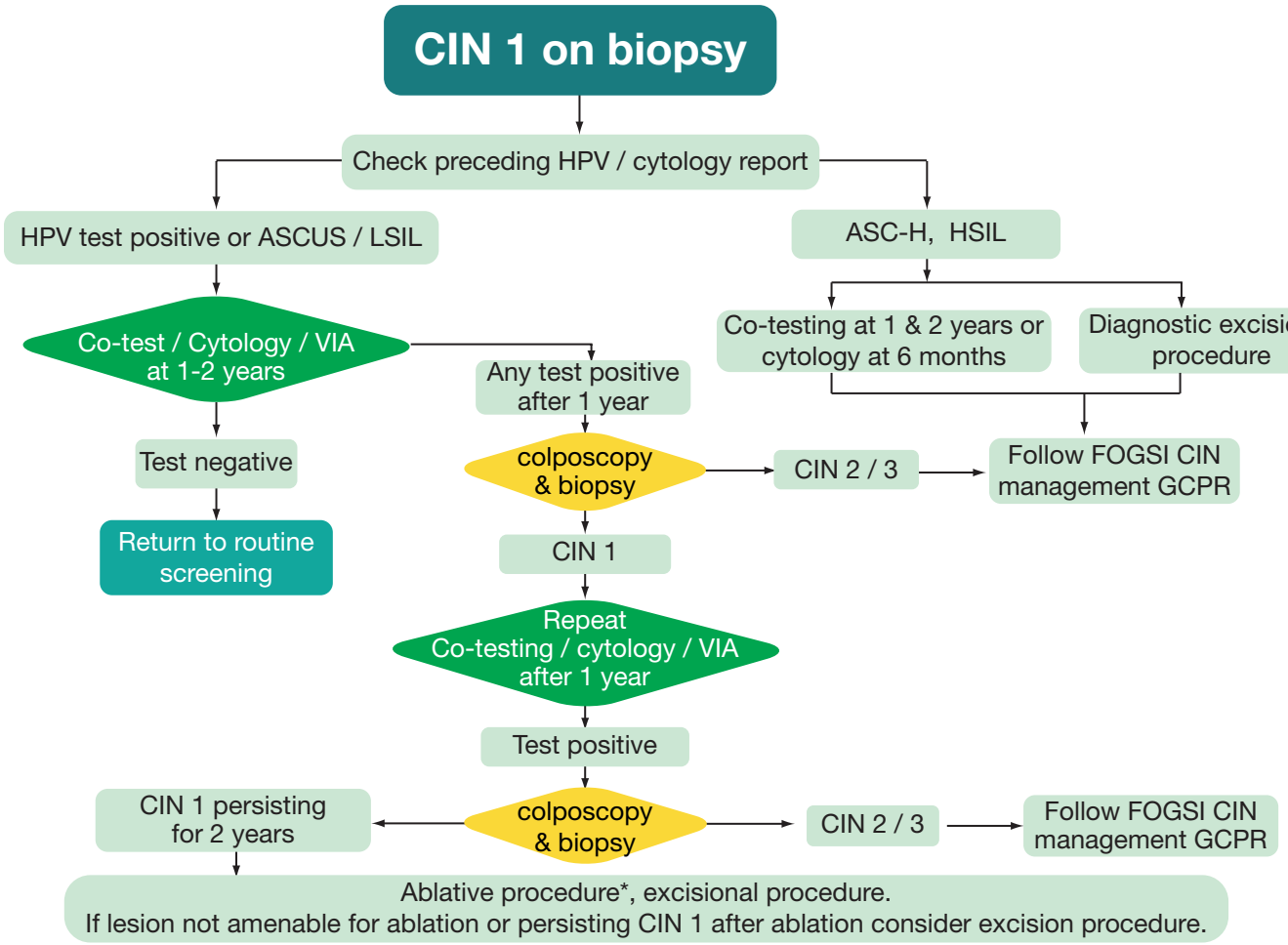


Chart 12

Management of women with CIN 1 on histology



*** Eligibility for Ablative Procedures**

1. Lesion should be entirely visible and occupy not more than two quadrants of cervix
2. Entire lesion should be located on ectocervix without any vaginal and/or endocervical extension
3. Lesion can be adequately covered by largest cryotherapy probe available
4. There is no suspicion of invasive cancer

Chart 13

Management of women < 30 years desirous of pregnancy with CIN 1 on histology

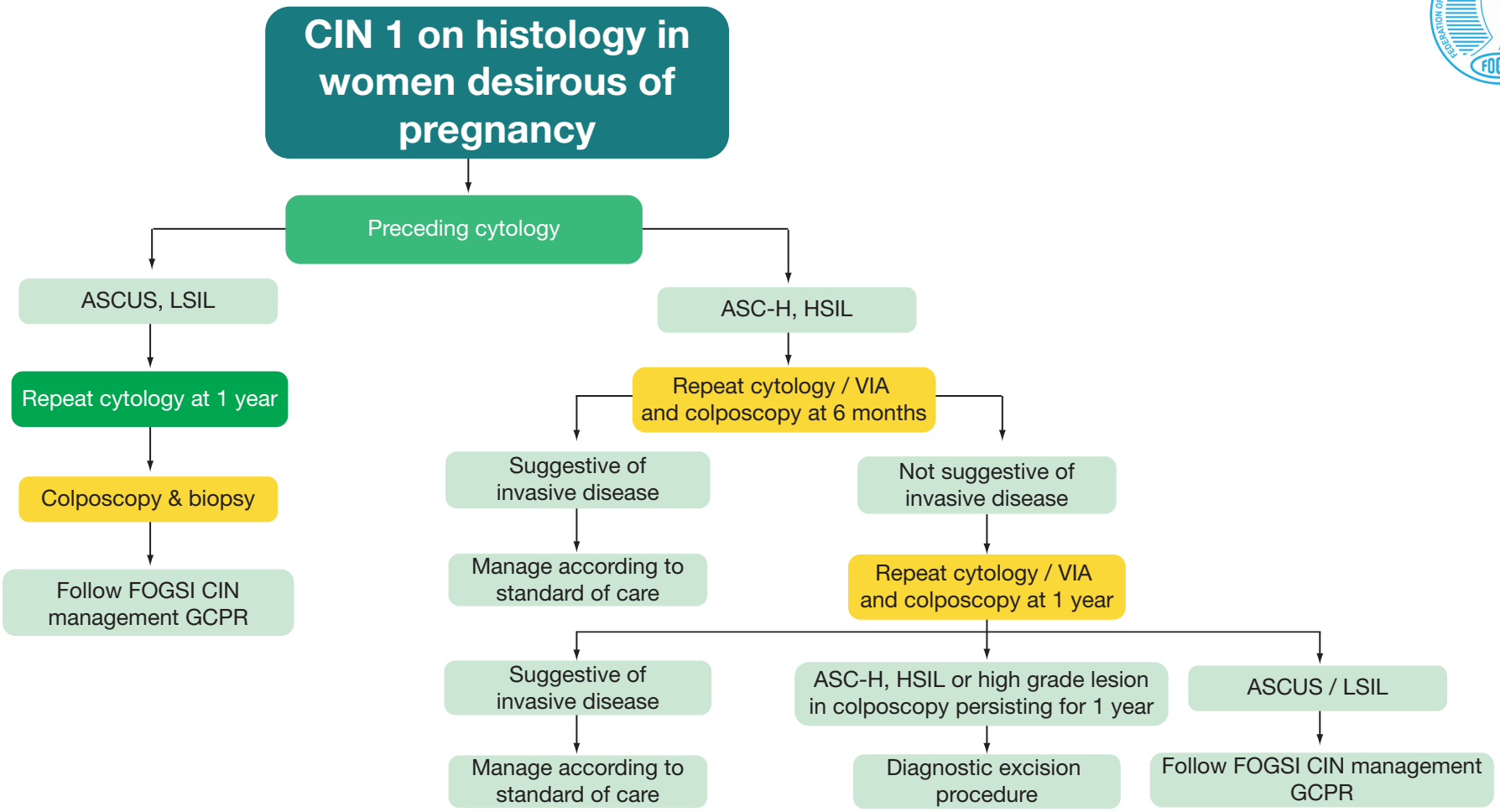
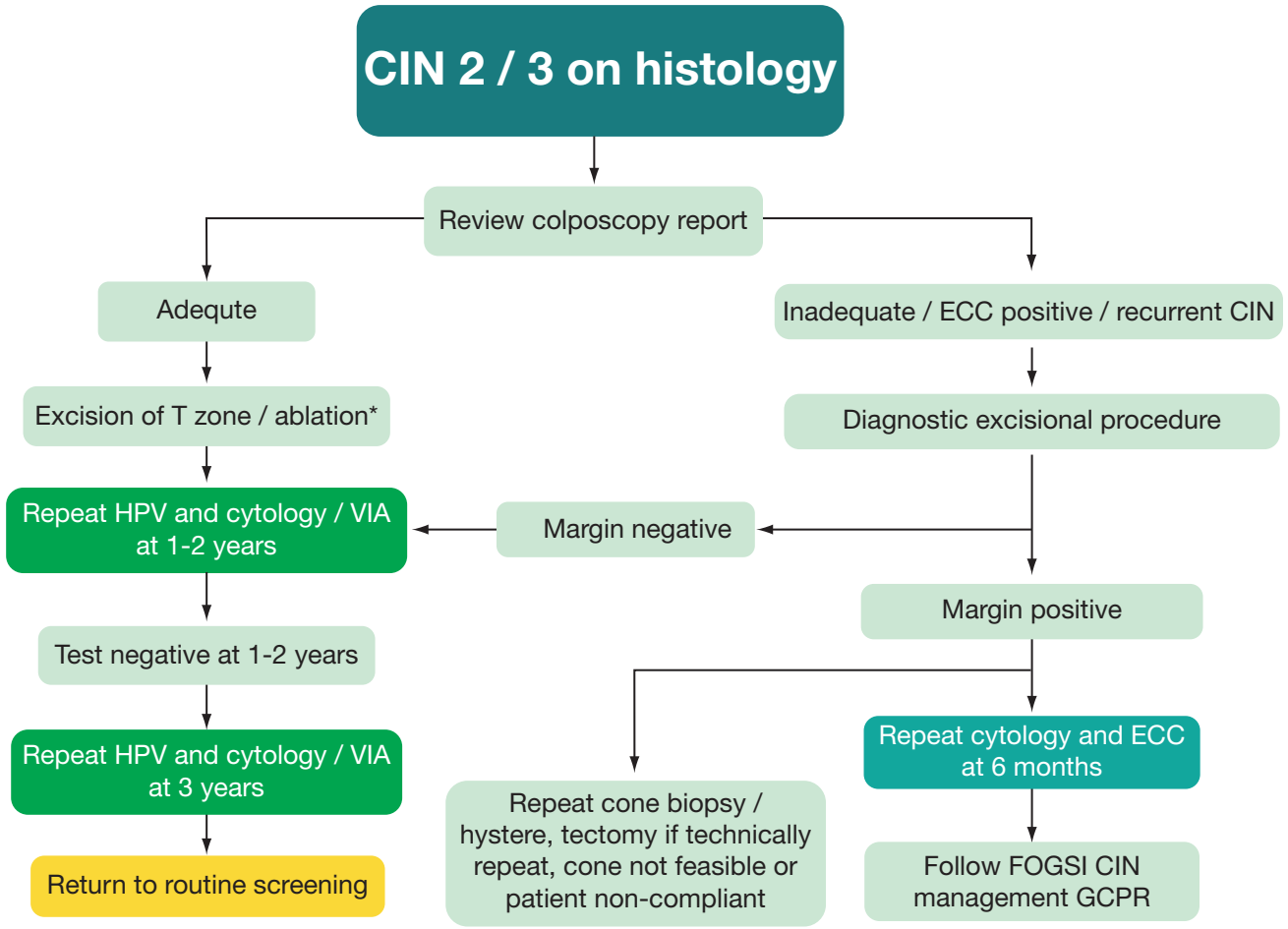


Chart 14

Management of women with CIN 2, 3 on histology



*** Eligibility for ablative procedure:**

1. Lesion should be entirely visible and occupy not more than two quadrants of cervix
2. Entire lesion should be located on ectocervix without any vaginal and/or endocervical extension
3. Lesion can be adequately covered by largest cryotherapy probe available
4. There is no suspicion of invasive cancer

N.B. In CIN 3, excision is preferred especially for large lesions, lesions not fully accessible for ablation, or recurrent lesion

Management of women with CIN 2, 3 on histology, desirous of pregnancy

Chart 15

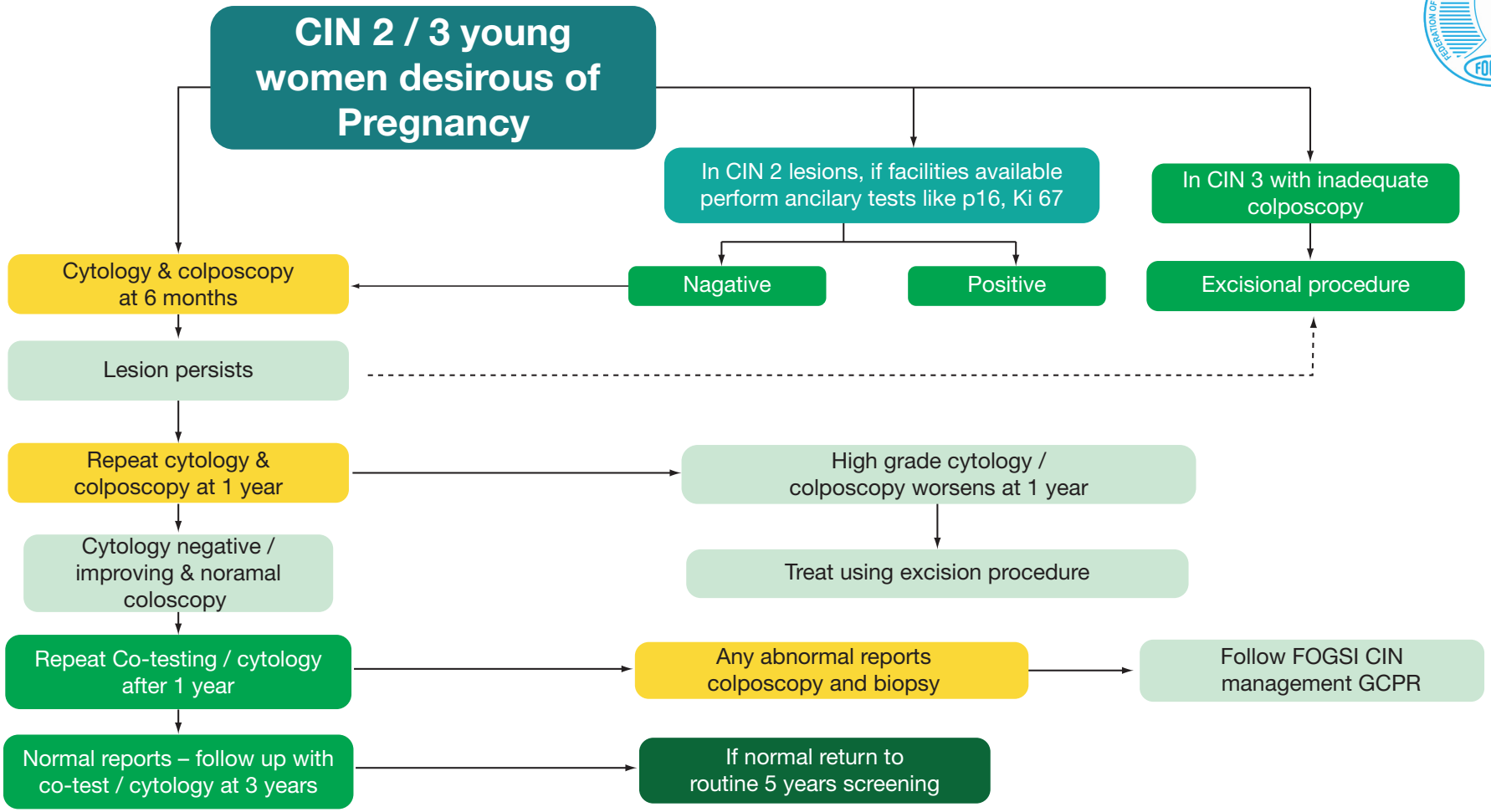
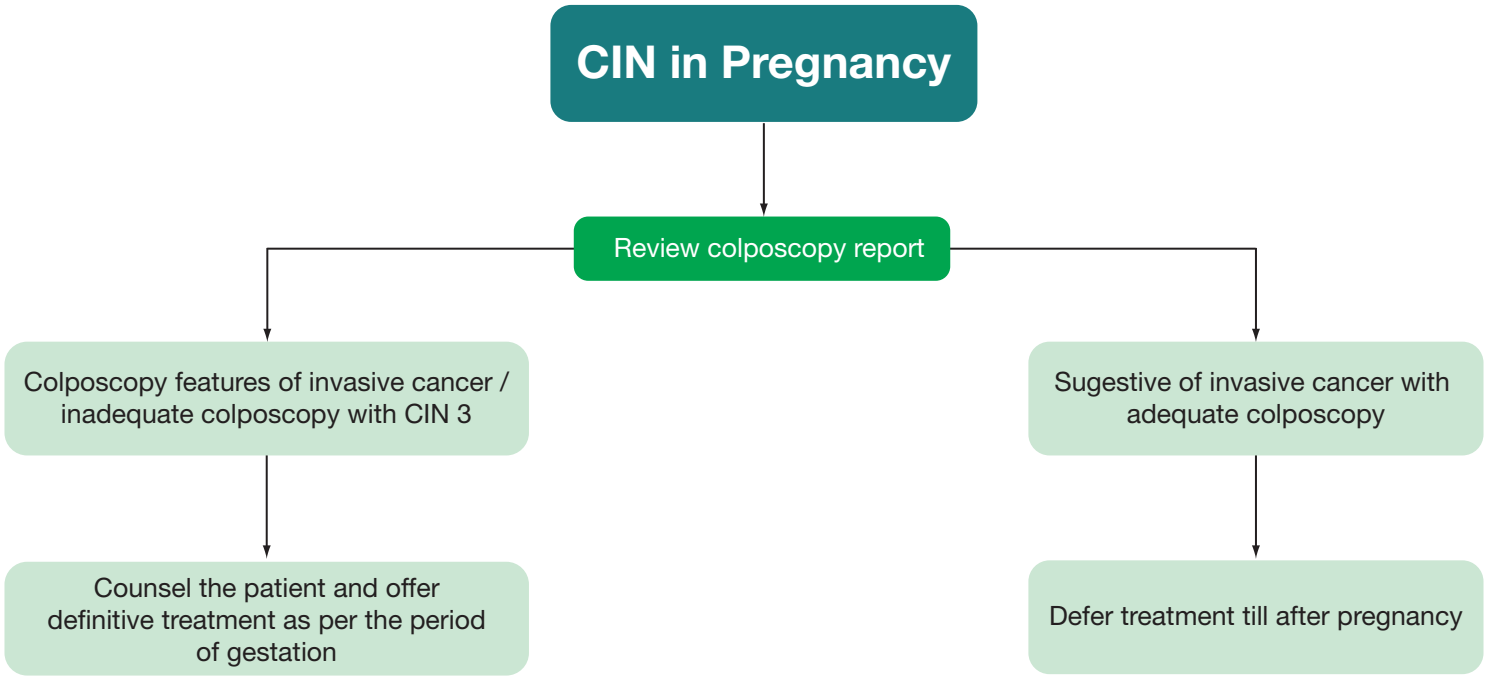


Chart 16

Management of women with CIN in Pregnancy



NEWER MODALITIES: PAP-BASED SCREENING		
Options	Liquid-based cytology (LBC) (Thin Prep, Sure Path)	Biomarkers (p16INK4a : CIN tec, (p16INK4a+Ki-67 CIN tec PLUS)
Advantage	Few inadequate Pap samples (1.9%), Benefits of Reflex HPV testing, automated reading possible	Identify transforming HPV infection, predict progression to CIN 2+ disease Triage low-grade smears Can be done with histology and cytology slides Reduce colposcopy referrals
Efficacy	Sensitivity not better than conventional (RR 1.1);11% more sensitivity for LSIL + lesions	Sensitivity:64-92%, Specificity: 41-96% for low-grade smears
Limitations	More expensive, not cost-effective. Automated not effective	Wide variation in reported sensitivity, lack of standardized reporting Need for substantial expert False positive rates high

NEWER MODALITIES: HPV BASED SCREENING				
Options	**Vaginal Self collection (eg. Delphi device, Evalyn sampler)**	**E6 E7 mRNA (APTIMA), APTIMA HPV GT**	**DNA Methylation (DNAme) Eg. QIAsure Methylation Test by Quiagen**	**Topoisomerase IIA (TOP2A) and MCM2** Markers of aberrant S-phase induction
Advantage	Acceptable, eliminates cost of visiting a clinician	Effective triage for low-grade smears, reduce colposcopy referral by 68% compared to 30% by HPV DNA testing	Alternative triage for hrHPV, automated, objective test, run on the same sample as the HPV assay	Identify transforming HPV infection
Efficacy	Sensitivity variable: 60-90% Overall 3.4 (95% CI=2.4-4.9) times more CIN 2+ detected by self-collected HPV samples than by routine cytology.	Sensitivity: 90-95%, Specificity: 42-61%, PPV: 67%	CADM1-m18 combined with MAL-m1 methylation: Sensitivity: 60.5%- 100%, Specificity: 22.7% to 83.3% (95% CI: 78.4-87.4).	Sensitivity: 67-99% , Specificity: 61- 85%.
Limitations	Inadequate sample, Woman-dependent, reluctance to use medical devices	Expensive	Expensive, wide variation in reported sensitivity	Research settings

HPV VACCINATION

FOGSI GCPR: HPV Vaccination

	FOGSI RECOMMENDATION	STRENGTH OF RECOMMENDATION
Presently licensed vaccines	Bivalent (Cervarix, GSK) Quadrivalent (Gardasil, Merck)	NA
License to use in India	9 - 45 years	NA
Preferred target age group	9 - 14 years	Grade A
Number of doses for girls aged < 15 years, not immunocompromised	2 doses	Grade A
Number of doses for girls aged ≥ 15 years or immunocompromised	3 doses	Grade A

FOGSI GCPR: HPV Vaccination

	FOGSI RECOMMENDATION	STRENGTH OF RECOMMENDATION
Interval	**Two doses:** At least 6 months, may be up to 12-15 months **Three doses:** 0,1,6 months (Bivalent) 0,2,6 months (Quadrivalent)	Grade A
Catch-up vaccination (15-26 years)	• 3 doses • Girls/ women who have been sexually active should be counselled regarding **reduced** efficacy and importance of **screening** from the age of 25-30 years (Not to be considered in public programs unless resources are available after vaccinating and screening the respective target age groups)	Grade B
Older age groups (> 26 years)	• 3 doses • Women aged > 26 years who have been sexually active should be counselled regarding reduced efficacy in older age group and the importance of screening • In limited-resource settings, women in this age group should first invest in screening	Grade B

FOGSI GCPR: HPV Vaccination (Special situations)

	FOGSI RECOMMENDATION	STRENGTH OF RECOMMENDATION
HIV positive or immunocompromised girls	• Same age recommendation • Three doses	Grade A
Interrupted doses	• Continue with the remaining doses as per age-based recommendation, vaccination series need not be restarted	Grade B
Pregnancy and lactation	• Not recommended	Grade B
Victims of sexual abuse	• Three doses • Initiate preferably at the time of examination at health care facility	Grade B
Women with history of abnormal screening reports	• Same age recommendation	Grade B
Males	• Not licensed for use in India at present	-

ABOUT PSI

PSI India is a non-profit, non-governmental organisation enabling people of India to lead healthier lives and plan the families they desire by marketing affordable products and services. We assist and complement the efforts of the Government of India (GoI) in the priority areas – Family Planning, Non Communicable Diseases including Cervical Cancer Prevention, Maternal and Child Health, Sanitation and Gender-based Violence. We use social marketing models and enable quality products and services to reach people at a price they can afford. We apply commercial strategies to the non-profit health sector, allowing women to access care in a place that is convenient, and in a way, they can understand. We are one of the largest organisations in India with many human assets working in several States and Union Territories across India. We believe in creating healthy communities and working conditions.

Management and Coordination: Ms. Deepti Mathur, *Senior Specialist, Knowledge Management, PSI*
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