

CIN2 IN CLINICAL PRACTICE

~~FINDING THE RIGHT BALANCE IN TREATMENT~~

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CLASSIFICATION OF PREINVASIVE CERVICAL DISEASE

Dysplasia (Richart,1973)	CIN (WHO 1975,2003)	Lower Anogenital Squamous Terminology (LAST;2012)
MILD	CIN 1	LSIL
MODERAE	CIN 2	HSIL
SEVERE	CIN 3	
CIS (Carcinoma In Situ)		

CIN II SHOWS HIGH SPONTANEOUS
REGRESSION RATE (42% AND 50% AT 12 AND 24
MONTHS, RESPECTIVELY), PARTICULARLY IN
YOUNG WOMEN (< 30 YEARS) (BMJ
2018;360:K499)

CIN II PROGRESSION RISK TO CIN III OR WORSE
INCREASES WITH TIME (FROM 5% AT 3 MONTHS
TO 24% AT 36 MONTHS) (BMJ 2018;360:K499)

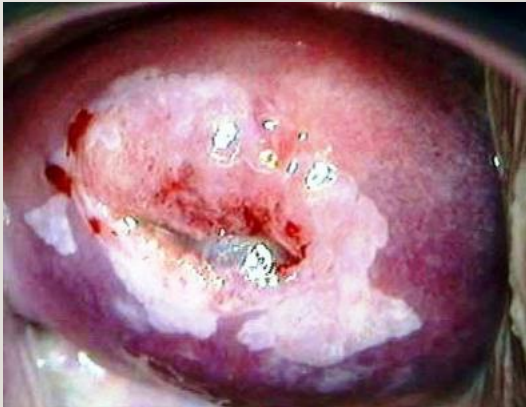
GROSS DESCRIPTION

- Predominantly flat lesions
- Hard to identify without acetic acid application

BEFORE ACETIC ACID



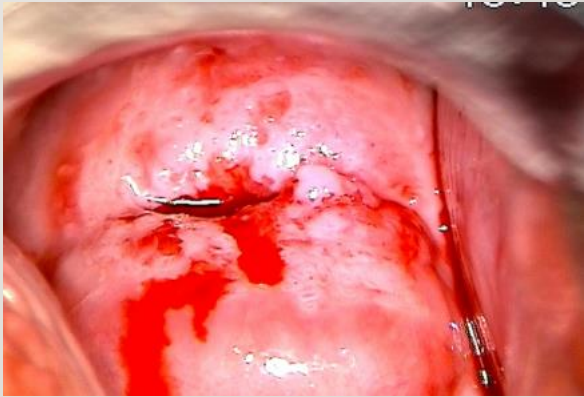
AFTER ACETIC ACID



BEFORE



AFTER



2014 WHO CLASSIFICATION: TERMINOLOGY FOR HPV-ASSOCIATED PRECANCEROUS LESIONS OF THE SQUAMOUS EPITHELIUM OF THE CERVIX.

2014 WHO classification	2003 WHO classification
<ul style="list-style-type: none">• Low-grade squamous intraepithelial lesion (LSIL)	CIN 1
<ul style="list-style-type: none">• High-grade squamous intraepithelial lesion (HSIL)	CIN 2 CIN 3

THE BETHESDA SYSTEM EPITHELIAL CELL ABNORMALITIES(2014):

(DEVELOPED IN 1988, THEN REVISED IN 1991, 2001 & LATEST 2014)

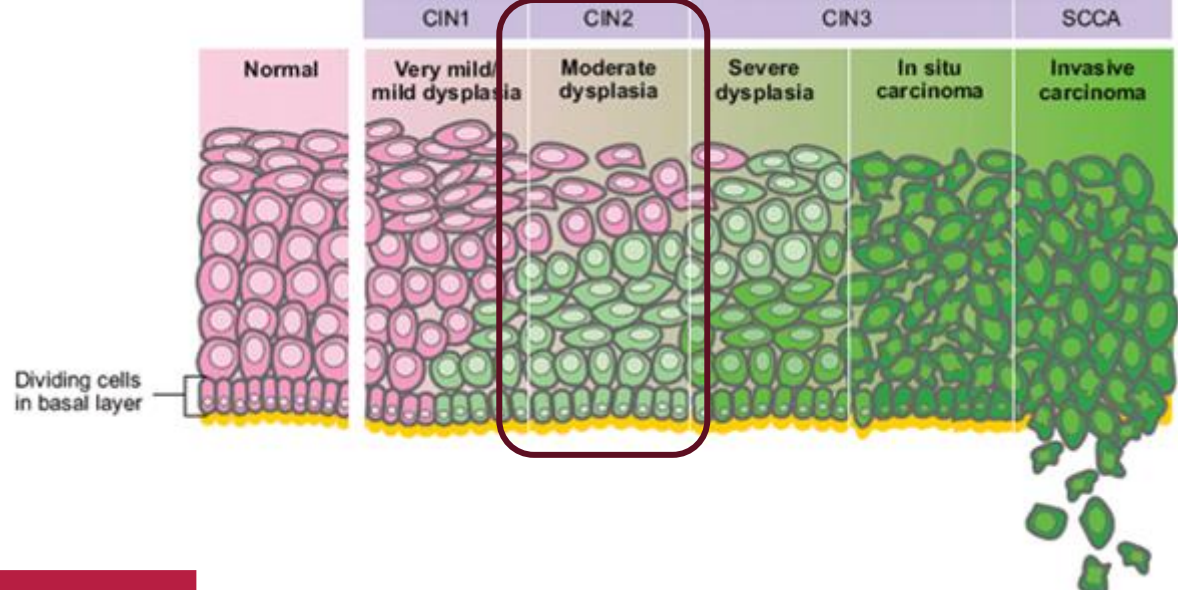
Squamous cell:

1. Atypical squamous cells of undetermined significance (**ASCUS**)
2. Atypical squamous cells cannot exclude HSIL (**ASC-H**)
3. **LSIL** (Mild dysplasia/CIN1)
4. **HSIL** (Moderate and severe dysplasia/ CIS/CIN 2 and CIN 3)
5. With features suspicious for invasion (if suspected)
6. Squamous cell carcinoma.

Glandular cell:

1. **Atypical:**
 - i. Endocervical cells NOS
 - ii. Endometrial cells NOS
 - iii. Glandular cells NOS
2. **Atypical**
 - i. Endocervical cells (Favor neoplastic)
 - ii. Glandular cells (Favor neoplastic)
3. **Endocervical Adenocarcinoma in situ**
4. Adenocarcinoma

CIN



CIN	Limit Of Histologic Changes
CIN 1	Basal one third of epithelium
CIN 2	Basal 50 to 75%
CIN 3	The entire thickness except one or two superficial layers

➤ HPV types 16 and 18 are associated with a higher risk of subsequent high-grade CIN.

➤ **The diagnosis, grading of dysplasia & CIN is highly subjective and not reproducible.**

COURSE OF CIN2

- It is not possible to accurately predict whether a woman will develop cervical cancer.
- **CIN 2 is more likely to spontaneously regress than CIN 3.**
- **There is an increasing tendency to follow CIN 2 lesions prospectively rather than treat, to permit the possibility of regression, particularly among young, nulliparous women.**
- **Reported progressive potential of histologically confirmed low-grade lesions to CIN 3 varies from 12– 33%.**

Cervical epithelium	CIN I	CIN II	CIN III
Regression (%)	60	40	30
Persistence (%)	30	35	50
Progression (%)	10	20	-
Invasion (%)	<1	5	20
Age of patient (in years)	25-30	30-35	40-45

IARC

Table 2.3: Regression, persistence and progression probabilities of CIN

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%	56%	-	12%

HPV interacts with genital tract squamous epithelia in two basic ways:

- **Firstly**, HPV infection may produce transient lesions, which support virion production. Such lesions have been variously described as low-grade lesions, intraepithelial neoplasia grade 1, mild dysplasia or condylomata.
- **Productive/Proliferative pattern**, Such lesions may be undetected clinically.
- Less likely to progress to invasive cervical carcinoma.

Secondly, HPV epithelial interaction may produce lesions classified as precancerous.

- Viral oncogene overexpression drives cell proliferation to produce a clonal expansion of undifferentiated cells, characterized clinically by persistent viral detection, persistent and advancing colposcopic abnormalities, and increasing risk of malignant transformation.

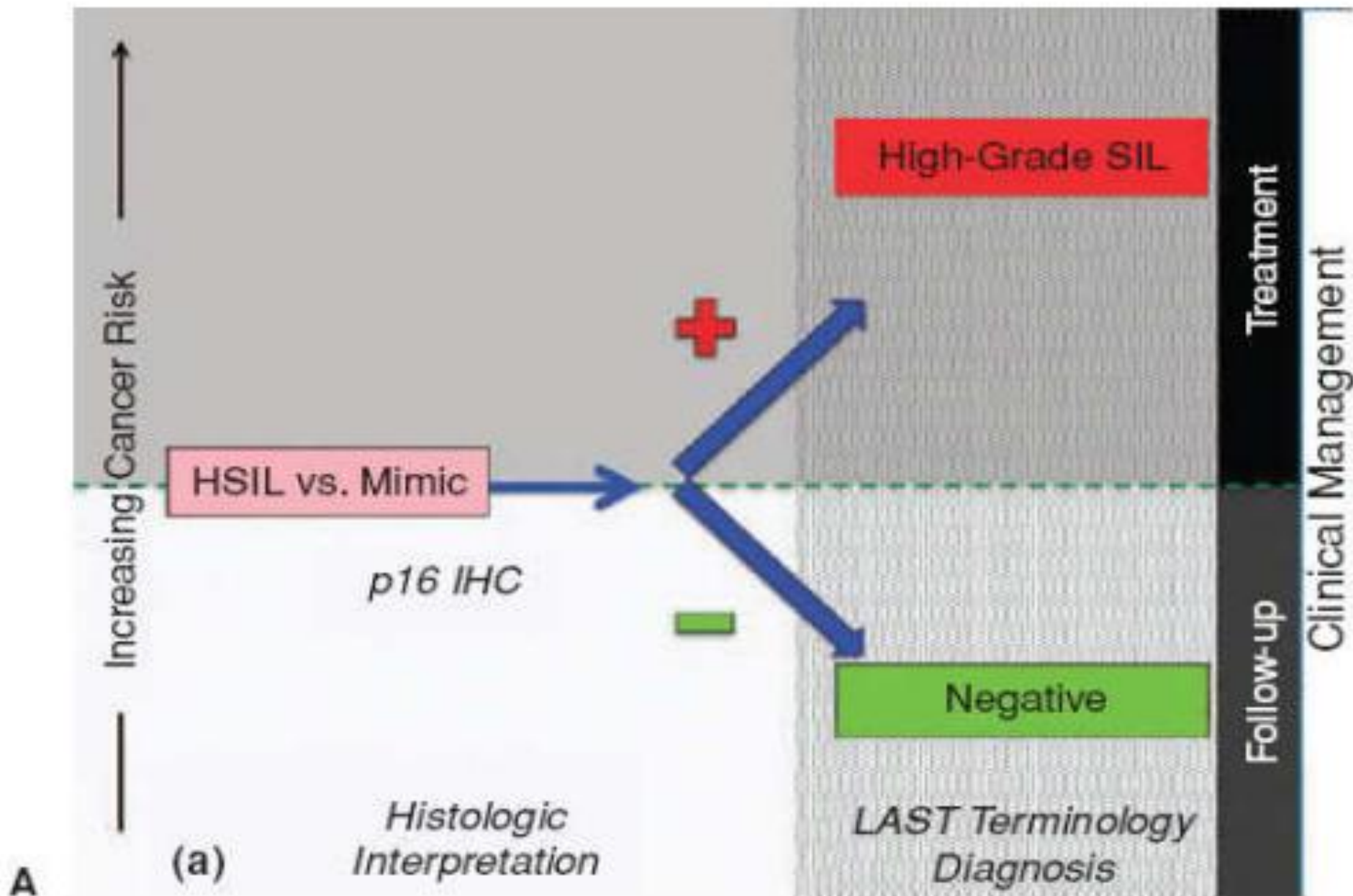
(Transformative/ Nonproliferative pattern)

- **CIN 3 has Transformative/ Nonproliferative pattern, more likely to progress to invasive cervical carcinoma.**
- **CIN 2 has combination of both pattern.**

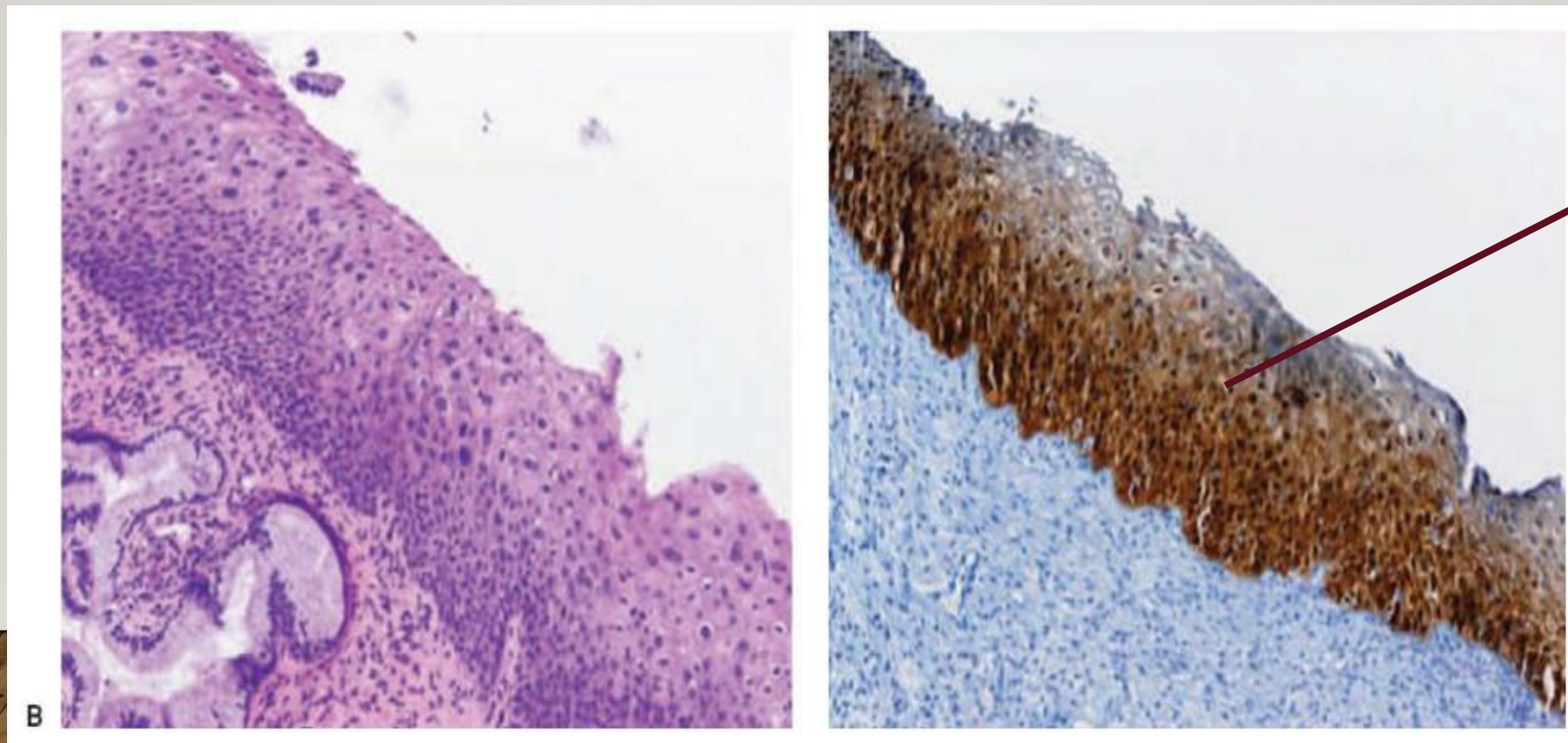
THE LAST PROJECT RECOMMENDATIONS:

1. ~~There should be a unified histopathologic nomenclature with a single set of diagnostic terms. A two-tiered nomenclature was recommended for noninvasive HPV-associated squamous proliferations of the lower anogenital tract, which may be further qualified with the appropriate –IN terminology. (intraepithelial neoplasia terminology without specifying location.)~~
2. HPV-associated squamous lesions of the lower anogenital tract should be classified as **low-grade squamous intraepithelial lesion (LSIL)** and **high-grade squamous intraepithelial lesion (HSIL)**, which may be further classified by the –IN classification.

3. The biomarker p16
diagnosis is between
immature squamou

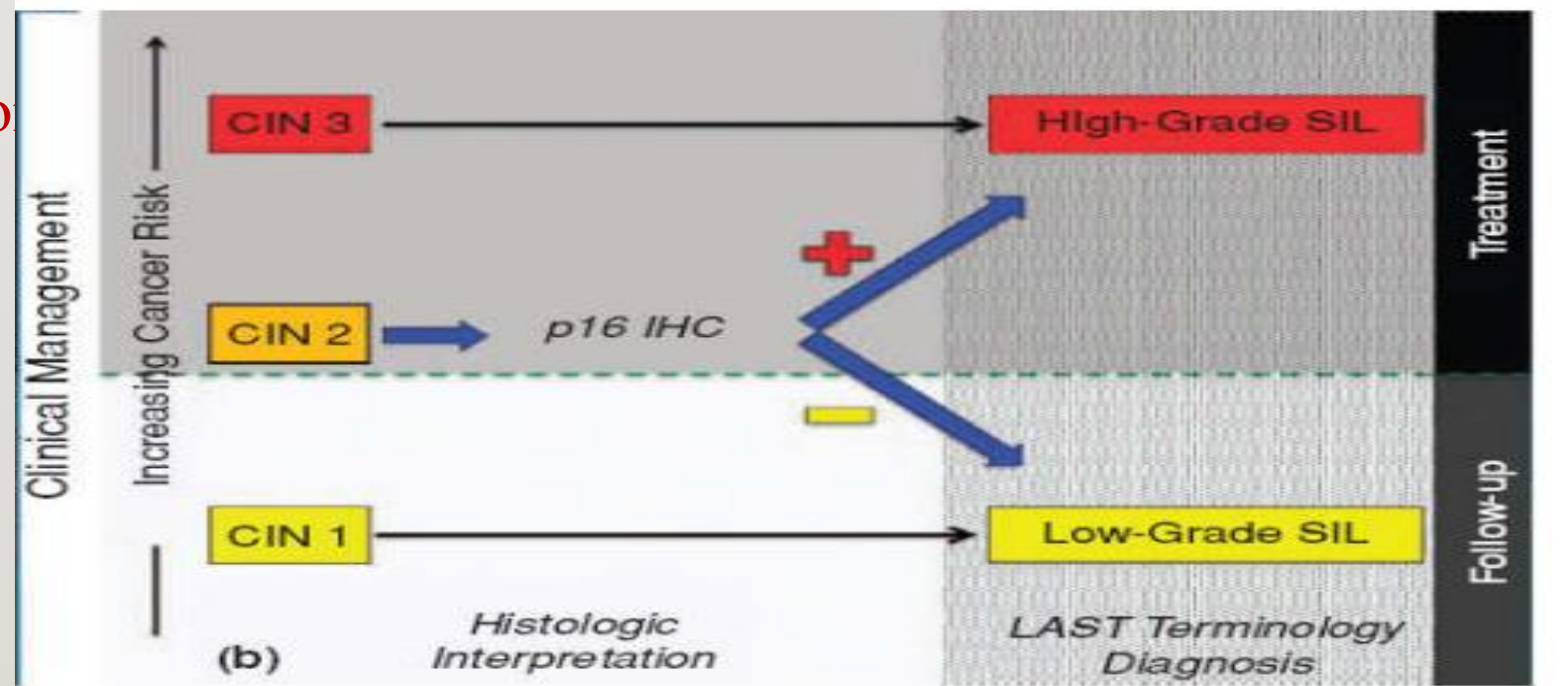


4. Strong and diffuse block-positive p16 results support a categorization of precancer.
- Negative or non-block-positive staining strongly favors an interpretation of low-grade disease or a non-HPV-associated pathology.



5. p16 IHC should be used as an adjunction tool for cases in which there is a professional disagreement in histologic specimen interpretation, that the differential diagnosis should include a precancerous lesion (–IN 2 or –IN 3).

- p16 positive CIN 2 combined with CIN 3 · high-grade lesion
- p16 negative CIN 2 co



6. p16 IHC should not be used as a routine adjunct to histologic assessment of biopsy specimens with morphologic interpretations of negative, –IN 1, and –IN 3.

- As a result of implementation of the recommendations of the LAST, p16 use has increased considerably, which **has resulted in an increase in the HSIL diagnosis rate, particularly in young women.**
- **To avoid overtreating young women,** observation may be recommended for HSIL requiring p16 IHC for confirmation.

Role of biomarker in diagnosing preinvasive cervical lesions:

- The most commonly applied is HPV 16/18 genotyping.
- HPV extended genotyping:
- Assays of RNA transcription, changes in viral and host genomes such as HPV E6 oncoprotein and p16(INK4A),
- Proliferation markers including Ki67,
- Methylation status of host genes and HPV genomes.
- **Dual IHC staining for the markers Ki-67 and p16** can improve histologic classification of CIN 3 abnormalities and resolve CIN 2 diagnoses .

GYNECOLOGY

Clinical course of cervical intraepithelial neoplasia grade 2: a population-based cohort study



Kathrine D. Lycke, MD; Johnny Kahlert, PhD; Rikke K. Damgaard, MSch; Dina O. Eriksen, MD; Mary H. Bennetsen, MD; Patti E. Gravitt, PhD; Lone K. Petersen, DMSci; Anne Hammer, PhD

Dec 2023

11,056 women underwent active surveillance, 6767 of whom regressed and 3580 of whom progressed within 24 months.

CONCLUSION: The observed high regression rates of cervical intraepithelial neoplasia grade 2 supported the transition in clinical management from surgical excision to active surveillance, particularly among women with low-grade or normal index cytology.

What does this add to what is known?

Our results support active surveillance for CIN2 in women planning for future pregnancy, particularly in women with normal or low-grade index cytology.

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PATHOLOGY OF THE LOWER GENITAL TRACT: ORIGINAL ARTICLES

The Lower Anogenital Squamous Terminology Standardization Project for HPV-associated Lesions

Background and Consensus Recommendations From the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology

Darragh, Teresa M. M.D.; Colgan, Terence J. M.D.; Thomas Cox, J. M.D.; Heller, Debra S. M.D.; Henry, Michael R. M.D.; Luff, Ronald D. M.D.; McCalmont, Timothy M.D.; Nayar, Ritu M.D.; Palefsky, Joel M. M.D.; Stoler, Mark H. M.D.; Wilkinson, Edward J. M.D.; Zaino, Richard J. M.D.; Wilbur, David C. M.D. For Members of the LAST Project Work Groups

TREATMENT MODALITIES FOR CIN2

- The treatment modalities for preinvasive cervical disease are:
 1. **Ablative procedures** : cryosurgery, thermal ablation and CO2 laser;
 2. **Excisional procedures**: including LEEP, excisional conization, CO2 laser excision,
 3. **Hysterectomy**
- Diagnostic excisional conization is now performed only for specific indications in which there remains a genuine risk of undisclosed invasive cancer.

CRYOSURGERY

- A simple, effective, inexpensive, and relatively easy therapeutic option.
- First introduced in 1968.
- Hypothermia is produced by the evaporation of liquid refrigerants, i.e. Compressed nitrous oxide (N₂O).
- It is allowed to expand through a small jet, producing an iceball at the surface of a metal probe placed in contact with the surface of the tissues to be frozen.
- Crystallization of intracellular water results in cell death.

CO2 LASER ABLATION OF THE TRANSFORMATION ZONE


- ~~Ideal choice for vaporizing sharply defined tissue volumes to a precisely determined depth .~~
- The entire TZ must be treated.
- To achieve optimal vaporization with minimal lateral thermal injury, the CO2 laser **should be used at the highest power output with which the surgeon is comfortable.**
- A minimum of 25 W but preferably above 60 W.
- The average power density must be kept within the range of 750 to 2,000 W/cm².
- Controlled tissue vaporization is achieved by delivering the laser energy in short bursts, either by use of the mechanical timer in the laser console or, preferably, by gating the laser pulses using the foot pedal.

THERMAL OR COLD COAGULATION

- Heat applied to the cervical epithelium induces tissue necrosis to an appropriate depth.
- Should be offered based on colposcopic assessment and diagnosis, after taking punch biopsies.
- There are several different probe shapes and sizes which can be chosen to best fit the topography of the TZ.
- Used In LMIC settings ,“see-and-treat” approach.

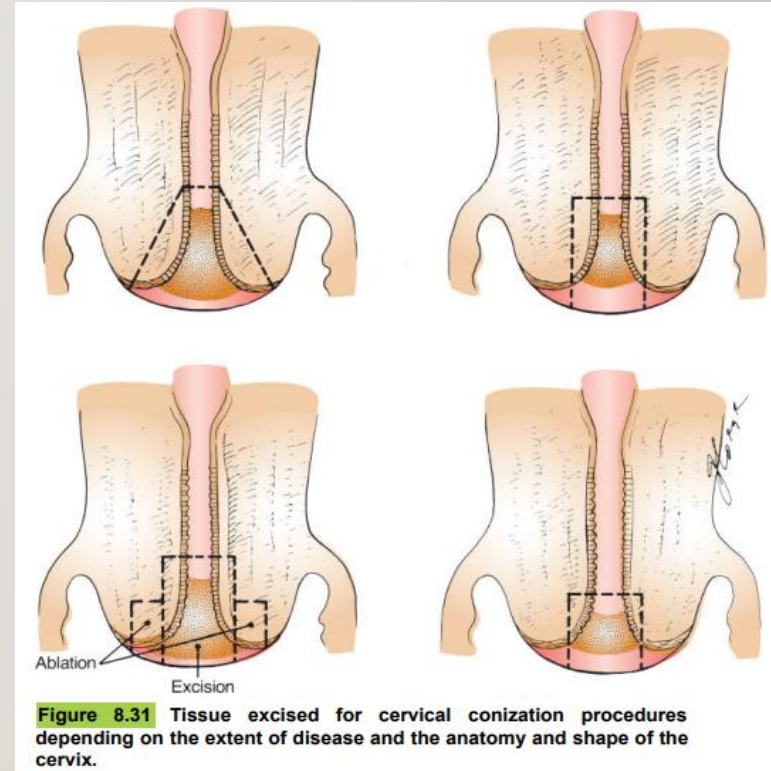


Advantages of Thermal coagulation over cryotherapy:

1. Treatment time is shorter;
 2. The equipment is light and portable;
 3. Morbidity is less;
 4. The electricity supply is more reliable than refrigerant gas refills, which are expensive and unreliable; battery-powered thermal coagulation devices further improve reliability;
 5. There is an absence of noise, smoke, and smell ; and
 6. The thermal coagulation applicator does not stick to the tissue during treatment.
- 

EXCISIONAL CERVICAL CONIZATION

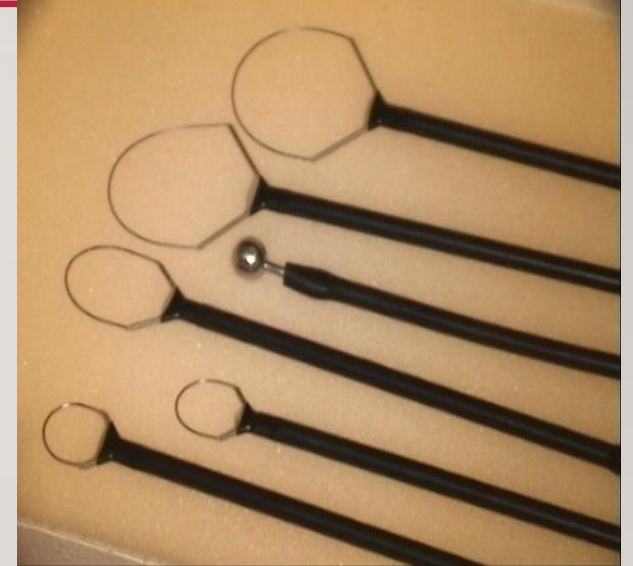
- ~~Excisional conization performed with a scalpel, “cold-knife conization”.~~
- It is both diagnostic and therapeutic.
- The geometry of the conization should adapt to the size and shape of the lesion as well as the geometry of the cervix .
- Excisional cervical conization achieves high cure rates for high-grade CIN.



- The risk of cervical stenosis and cervical incompetence is higher

LOOP ELECTROSURGICAL EXCISION PROCEDURE

- i. LLETZ (Large Loop Excision of the Transformation Zone)
- ii. LEEP (Loop Electrosurgical Excision Procedure)
 - First described by Cartier (LEEP), later Walter Prendiville (LLETZ)
 - Cut by vaporizing at 100°C
 - Coagulate by dehydrating ($> 100^{\circ}\text{C}$)
 - The procedure combines the advantages of conservative ablative procedures in preserving cervical tissue with the safety of histologic assessment of the entire lesion.



- Best loops 0.2 mm diameter
Tungsten/ steel

Indications

- Any grade of CIN
- Any type of TZ
- CIN lesions that cannot be treated by ablation
- See & Treat-High Grade Lesion with TZ 3 on Colposcopy .

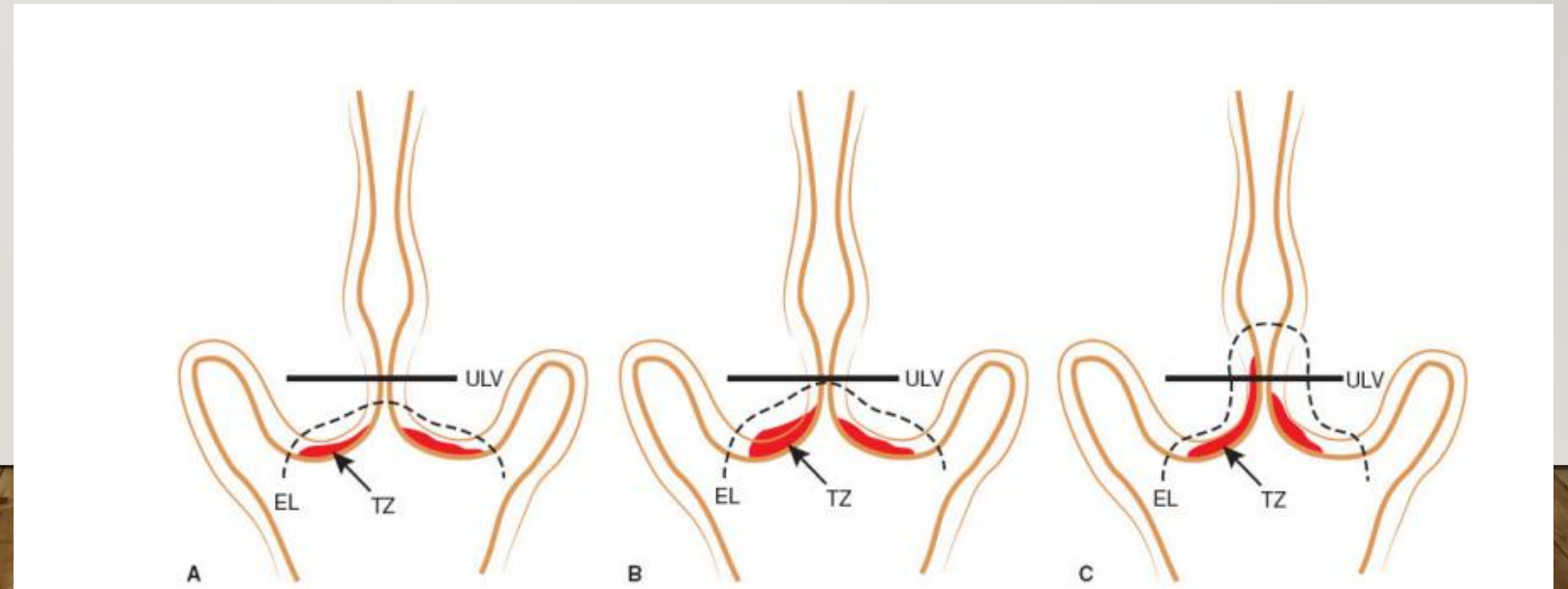
Contraindications

- Active vaginitis/cervicitis
- Suspected invasion/microinvasion
- Discrepancy between cytology, colposcopy & histology
- <3months post-partum

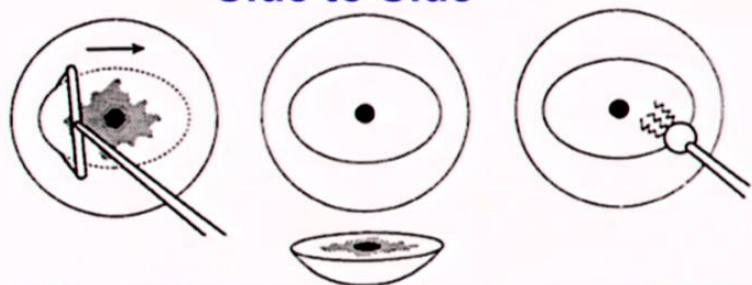
TYPES:

- Loop excisions are stratified as types 1, 2 or 3, according to the length of cervical tissue excised.

- **Type I excision** : Usually to 8 mm and not more than 10 mm length of cervical tissue excised.
- **Type 2 excision** : Not more than 15 mm length of tissue excised.
- **Type 3 excisions**: Equivalent to “cone biopsy” and >15 mm length.



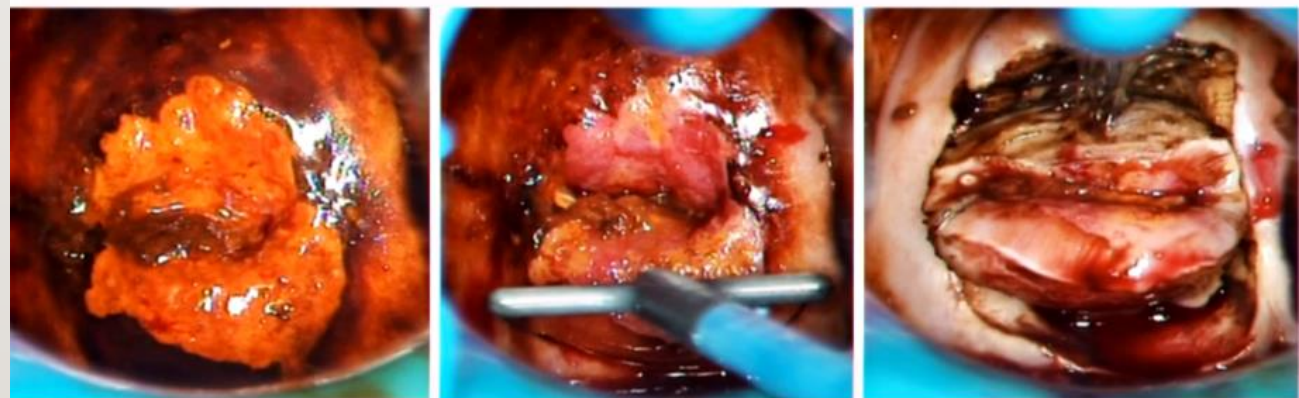
Direction of Treatment – Side to Side



International Agency for Research on Cancer



Direction of Treatment – From below upwards



Advantages of LEEP:

- The procedure is quicker and easier.
- Ability to “see-and-treat” at one visit.
- Patient acceptance is better.
- The entire specimen can be submitted for histologic study.

Complications:

- Are minimal.
- Postoperative bleeding occurs in 2–5% of patients. Postoperative infection is uncommon.
- Cure rates appear comparable with those achieved with CO2 laser procedures and with

“cold-knife” conization.

COMPARISON OF TREATMENT MODALITIES:

Table 8.12 Comparison of Treatment Modalities

<i>Procedure Rates</i>	<i>Technical Ease</i>	<i>Equipment Cost</i>	<i>Complication Rates</i>	<i>Primary Cure (%)</i>
Cryosurgery	+++	+++	++	80
Loop electrosurgical excision procedures	+++	++	+++	95
Laser ablation	++	+	+++	95
Laser excision	+	+	++	95
Cold-knife conization	++	+++	++	98

+, low benefit; ++, medium benefit; +++, high benefit.

HYSTERECTOMY

- Hysterectomy is rarely indicated in the primary management of CIN.
- The most common indication is coexistence of a gynecologic condition that warrants hysterectomy.
- Before any hysterectomy, colposcopic assessment should be performed.
- **If the entire lesion and TZ are not seen, or if there is any cytologic, colposcopic, or histologic suspicion of high-grade glandular neoplasia or invasive cancer, an excisional conization must be performed prior to hysterectomy.**
- High-grade vaginal intraepithelial neoplasia (VAIN) develops in the vaginal vault in 1–7% of patients who have undergone hysterectomy to treat CIN.

- If hysterectomy is performed for the management of CIN, the patient should have a vault smear and colposcopy on two occasions at 6 months and 18 months after surgery.
- Need to be screened with HPV at 6 months and 18 months.
- Screening following abnormal reports $>$ CIN 2+, irrespective of method of treatment, She should be screened 20 years thereafter.

(FOGSI GCPR 2023)

MANAGEMENT OF WOMEN WITH CIN2 IN PREGNANCY

- Pregnancy may be a woman's first opportunity to be screened for cervical cancer as part of

routine p

> Arch Gynecol Obstet. 2020 Jun;301(6):1503-1512. doi: 10.1007/s00404-020-05518-1.
Epub 2020 Apr 22.

- During p

Course of cervical intraepithelial neoplasia diagnosed during pregnancy

ing diagnosis on a

colposcop

Donata Grimm ^{1 2}, Isabelle Lang ³, Katharina Prieske ³, Anna Jaeger ³, Volkmar Müller ³,
Sascha Kuerti ³, Eike Burandt ⁴, Susanne Lezius ⁵, Barbara Schmalfeldt ³, Linn Woelber ³

Affiliations + expand

- If there i

PMID: 32322982 DOI: 10.1007/s00404-020-05518-1

oscopic diagnosis

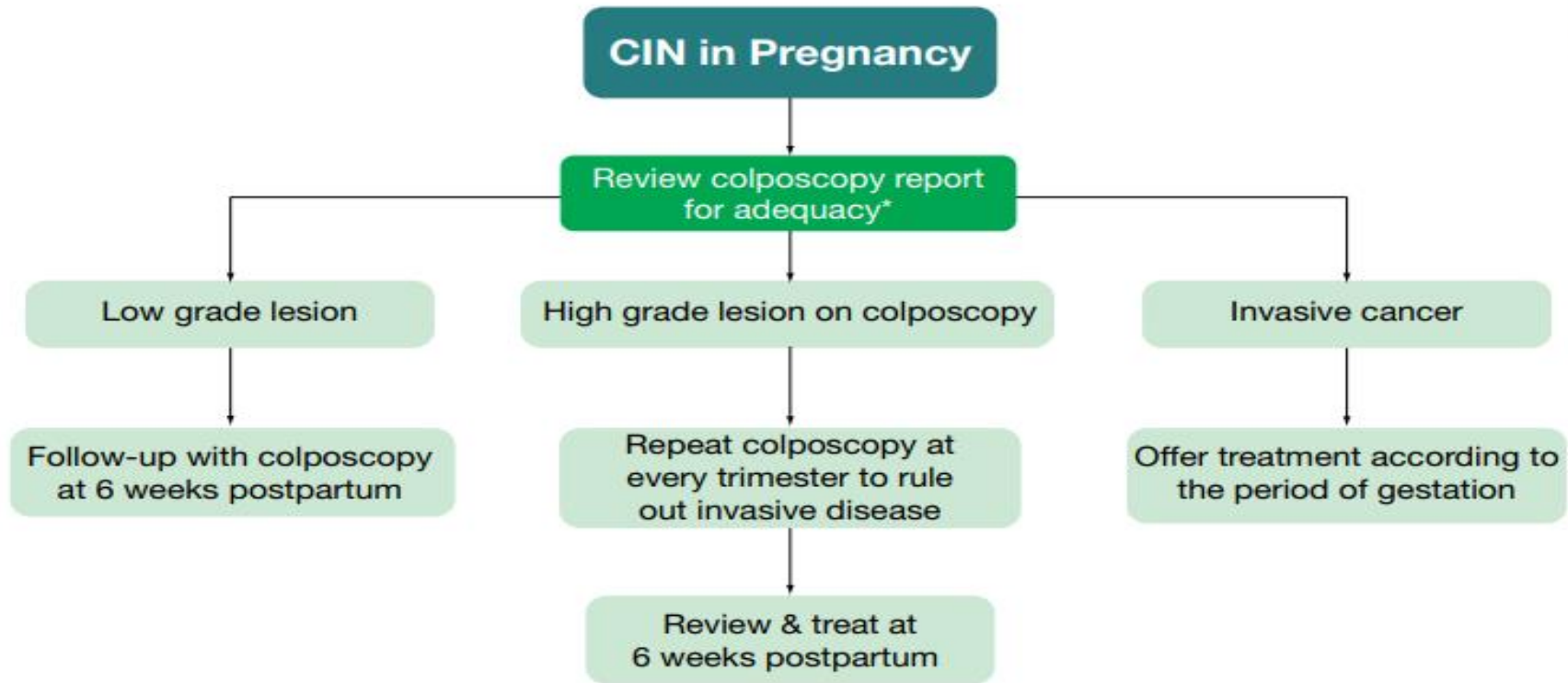
changes to a more severe degree of abnormality at any of the follow-up visits during

pregnancy, a directed punch biopsy should be obtained.



- **If the disease is stable**, the woman can be seen at 2 to 3 months post-partum for definitive diagnosis by biopsy and appropriate management of any lesion(s).
- Vaginal delivery can be allowed in confirmed CIN.
- These women should be seen for definitive reassessment at 8 to 12 weeks post-partum and treatment are planned.
- The cervix should be completely involuted and/or healed before re-colposcopy.
- The management plan at post-partum follow-up visits depend on the final diagnosis, and correspond to those described for nonpregnant women.

Management of Women with CIN in Pregnancy

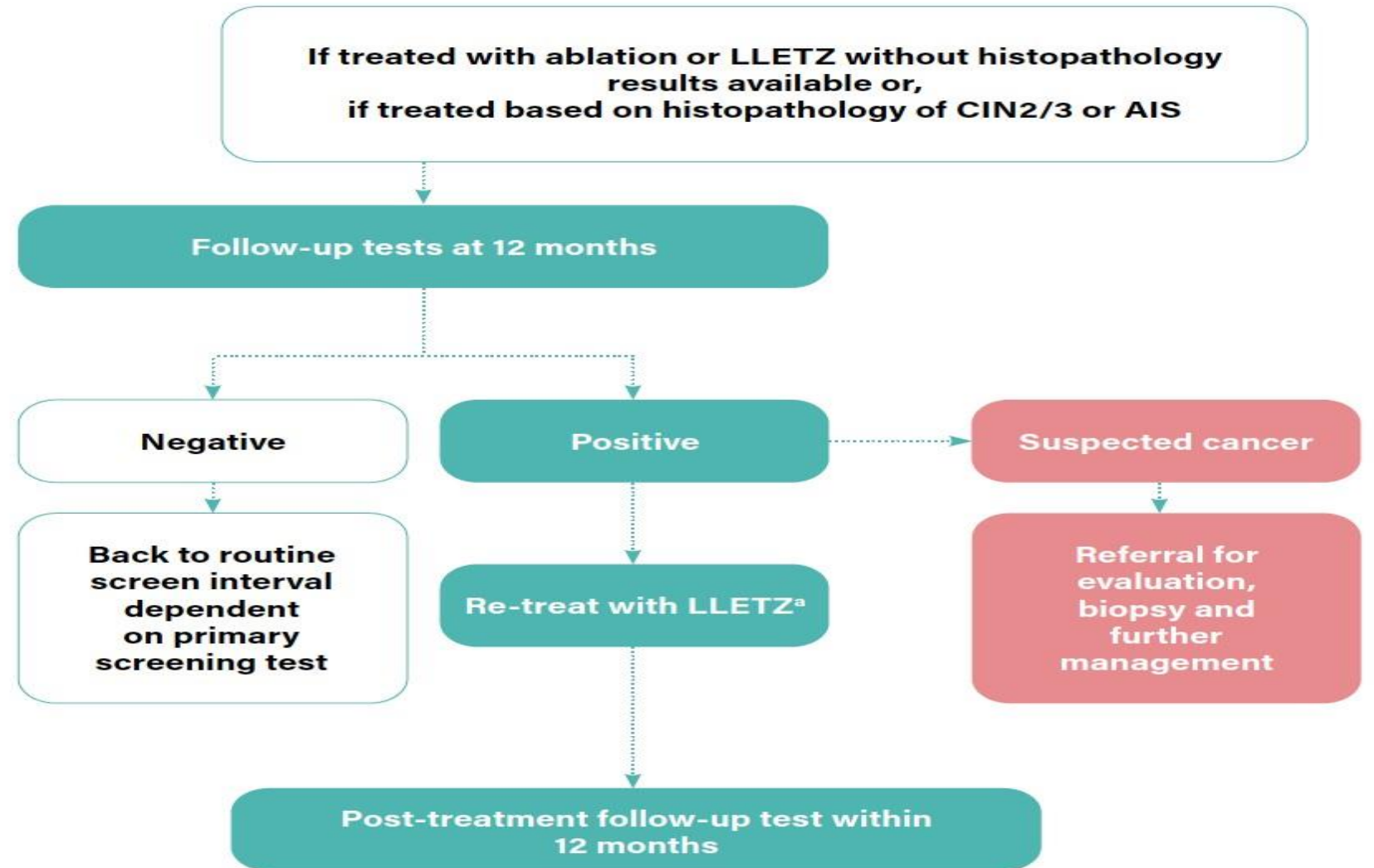


* ECC should be avoided in pregnant women

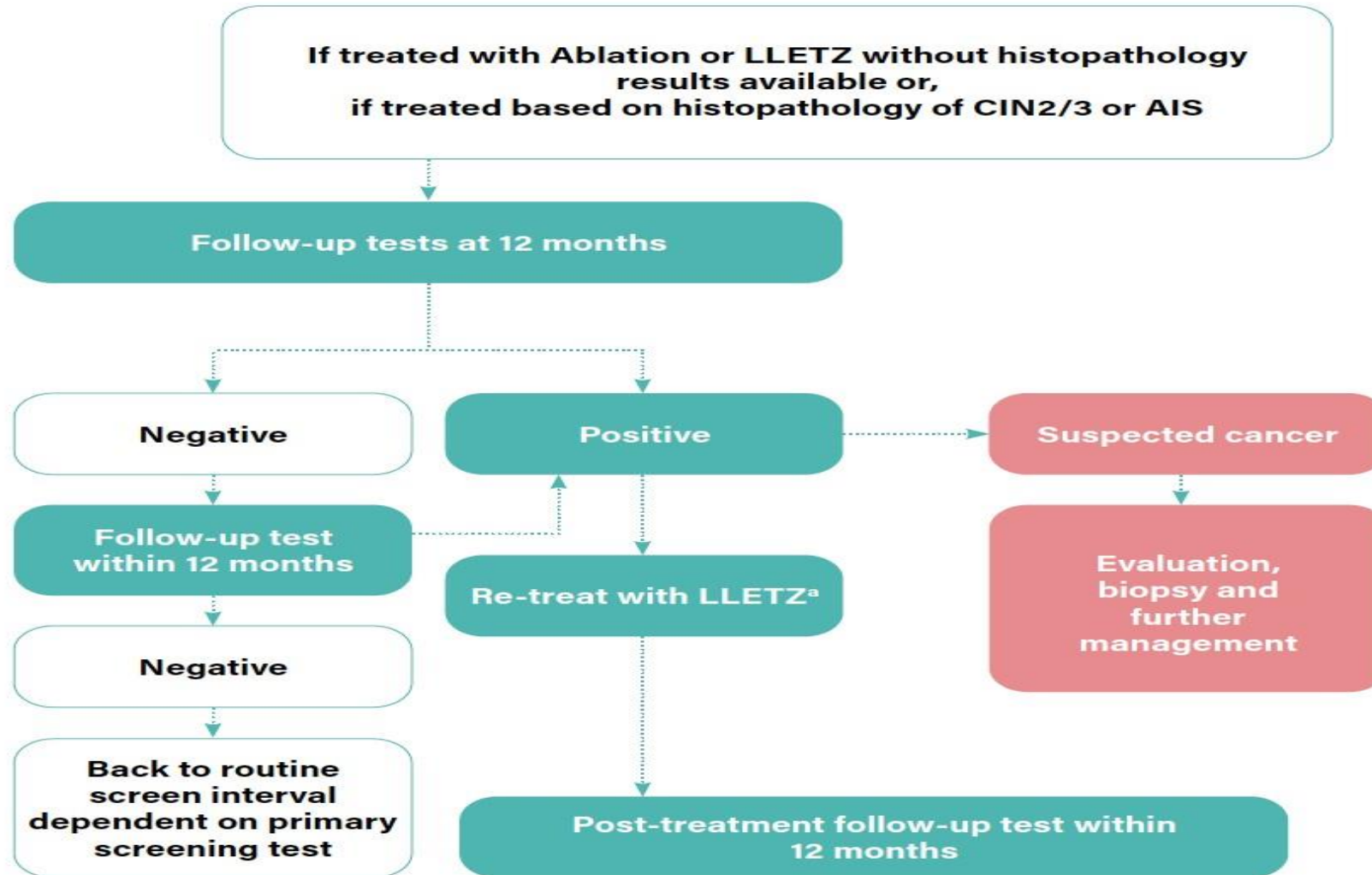
1. Diagnostic excision is advisable only if invasive cancer is suspected (Level A)
2. Defer post-partum evaluation to 6 weeks (Level A)

FOLLOW UP

FOLLOW-UP TESTS AT 12 MONTHS POST-TREATMENT FOR THE GENERAL POPULATION OF WOMEN



FOLLOW-UP TESTS AT 12 MONTHS POST-TREATMENT FOR WOMEN LIVING WITH HIV



THANK YOU

THANK YOU

