The Bethesda System and Guidelines for the Management of Cervical Intraepithelial Neoplasia

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Presentation Plan

- History of Smear Nomenclature
- The Bethesda System
- Adequacy of the Specimen
- ASCUS, ASC
- LSIL
- AGUS, AGC, AIS
- Algorithm

George N. Papanicolaou
New Cancer Diagnosis (1928)

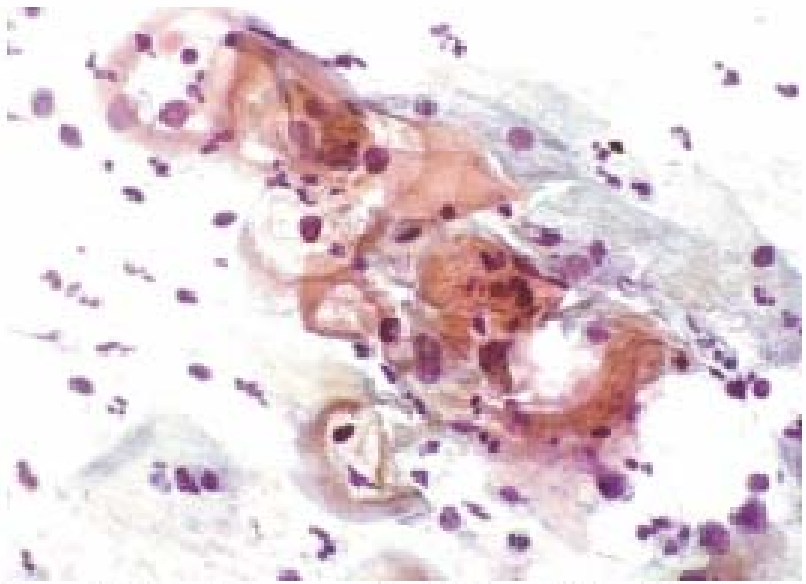


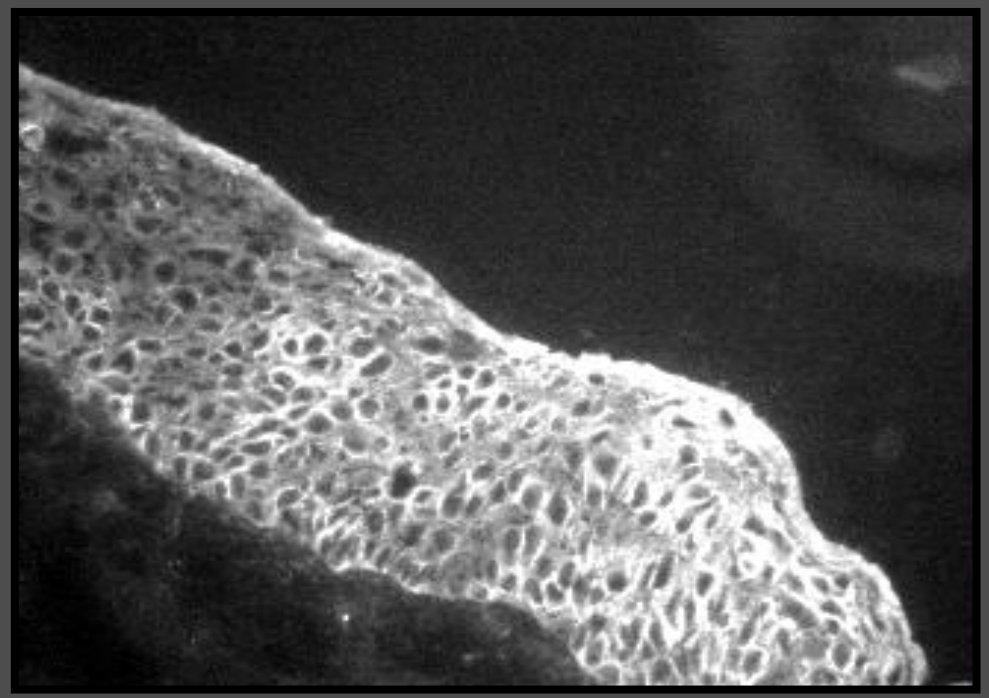
Figure 3–2. Papanicolaou smear classified as epithelial cell abnormality, low-grade squamous intraepithelial lesion. Some koilocytes are evident in this smear, characterized by slightly enlarged nuclei with somewhat irregular nuclear outlines and distinctive perinuclear haloes. Two binucleated squamous cells are also present.

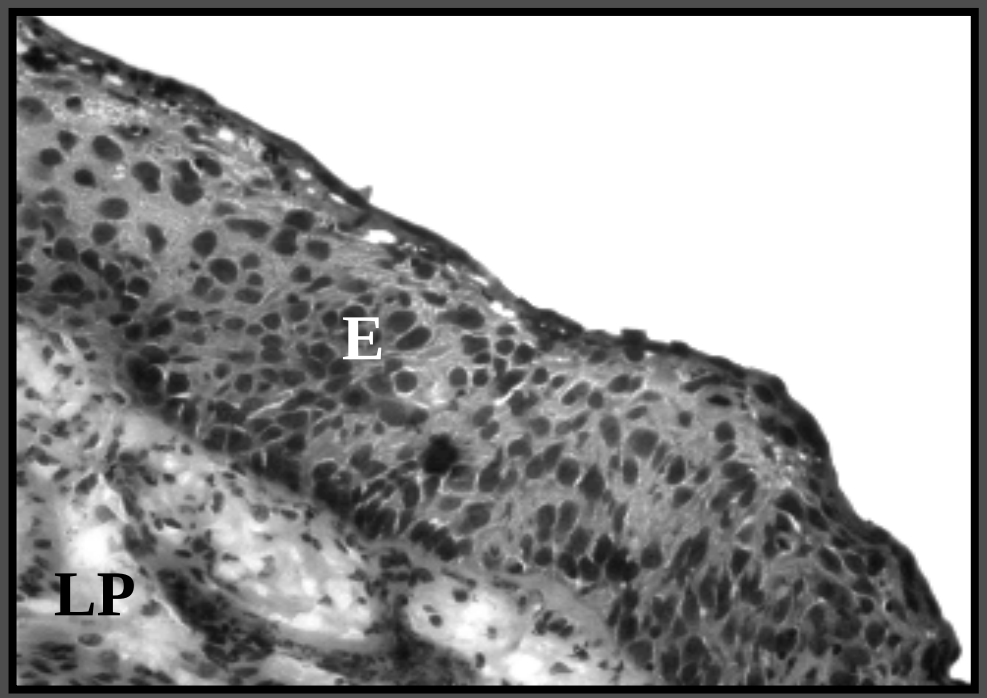
H. Traut, J.E. Ayre

SMEAR NOMENCLATURE

Pap (1954)	Descriptive (WHO) (1968)	CIN (1978)	Bethesda System (1988)
1	Negative for malignant cells	Negative	Within normal limits
2	Inflammatory atypia		Reactive and reparative changes
	Squamos atypia		ASCUS
	Koilocytotic atypia		LSIL; includes condyloma
3	Mild dysplasia	CIN 1	LSIL; includes condyloma
	Moderate dysplasia	CIN 2	HSIL
	Severe dysplasia	CIN 3	HSIL
4	Carcinoma in situ	CIN 3	HSIL
5	Invasive Carcinoma	Inv Ca	Invasive Carcinoma

Cin III 20x (exocol), h-ALA 0,5%, 75 min

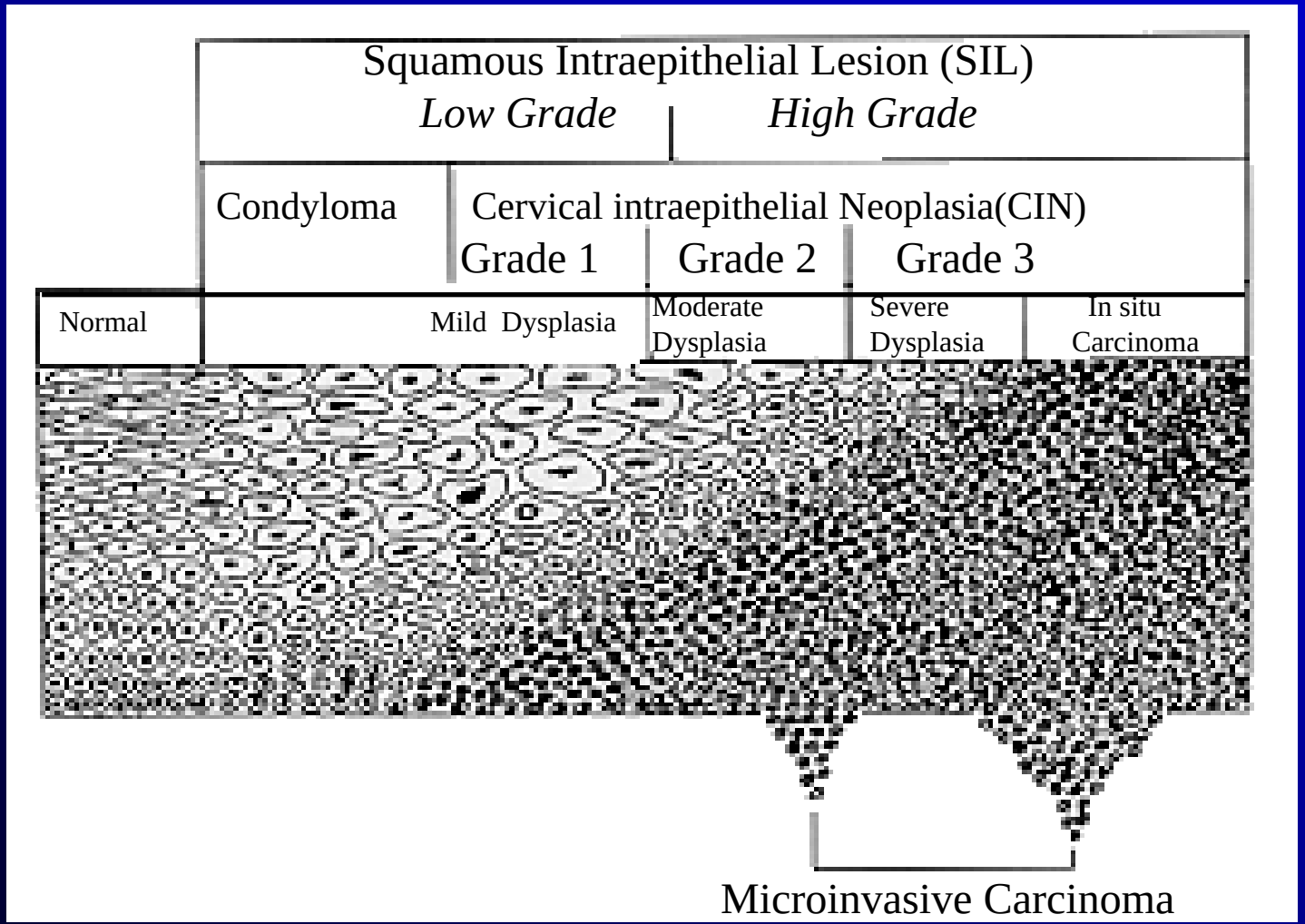




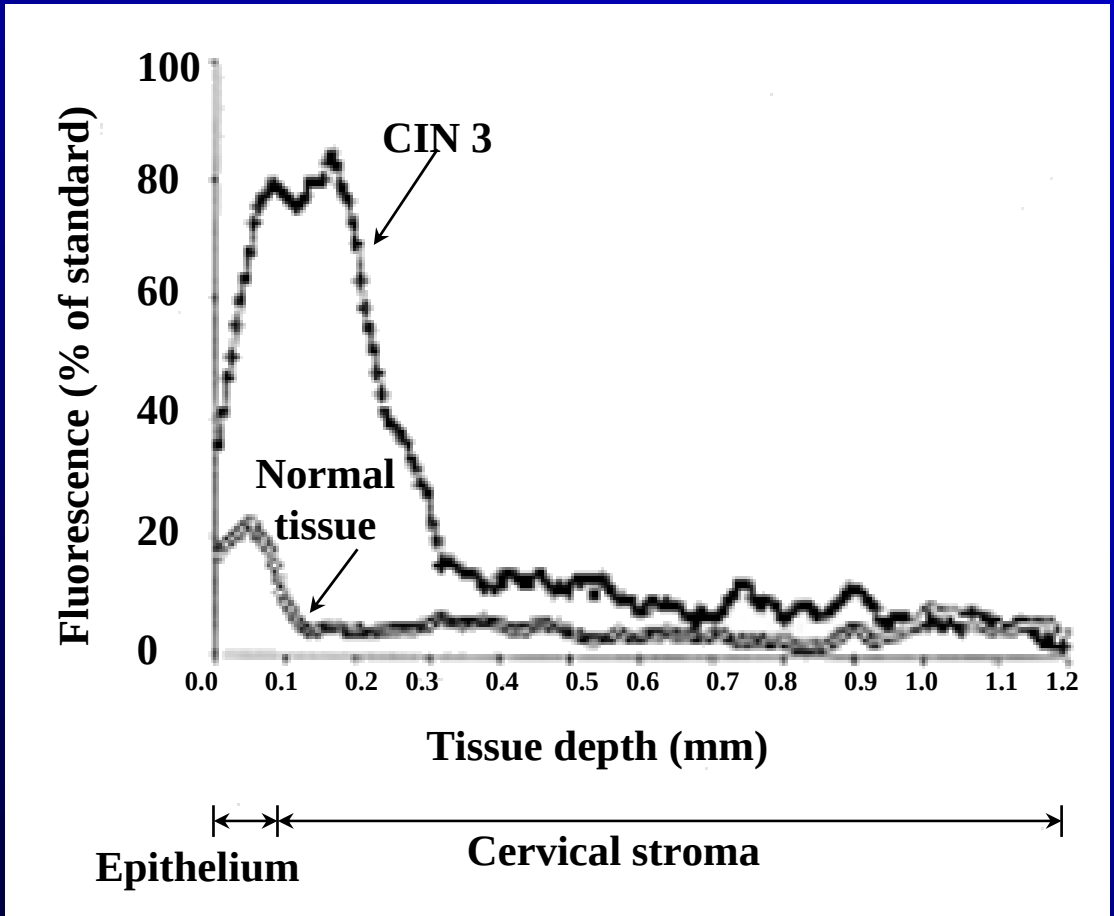
E- epithelium, LP-lamina propria

Départements de Pathologie Clinique et de Gynécologie et Obstétrique HUG & EPFL, mai 2002

Cervical squamous carcinoma precursors



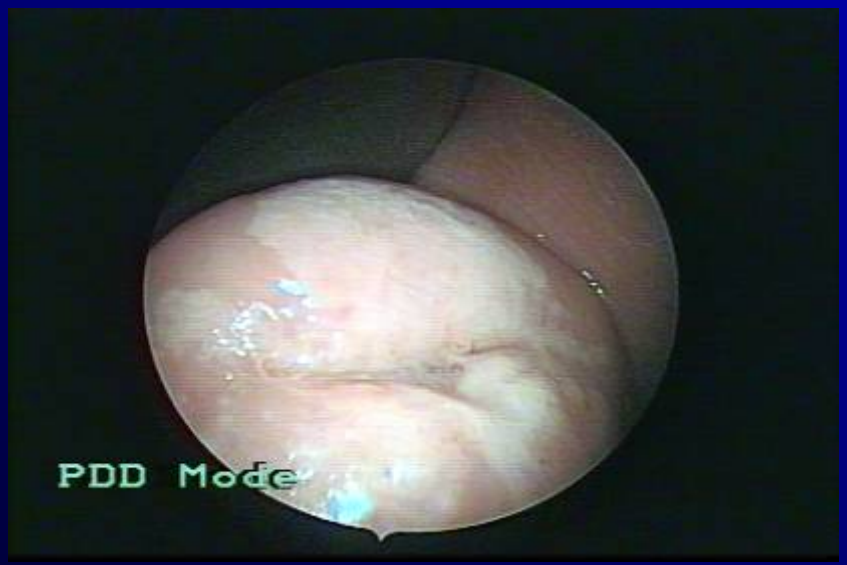
Thickness of HSIL of the cervix



Pahernik et al Int J Cancer 78 : 310-314, 1998

Fluorescence image of the cervix after h-ALA application

White light



Fluorescence

Fluorescence image and white light image of the cervix uteri after the application of 3% acetic acid. Application of 10mg h-ALA in 10ml 0.9% NaCl solution on the cervix during 3 hrs.

The Bethesda System (1988)

- The term *squamous intraepithelial lesion* is characterized by a high spontaneous regression rate and the lack of predictable progression of SIL to invasive cancer
- The Bethesda System replaced 3 levels of CIN with 2 levels, LSIL and HSIL, which could be used to describe any squamous abnormality of the lower genital tract

Summary of the Natural History of Cervical Intraepithelial Neoplasia

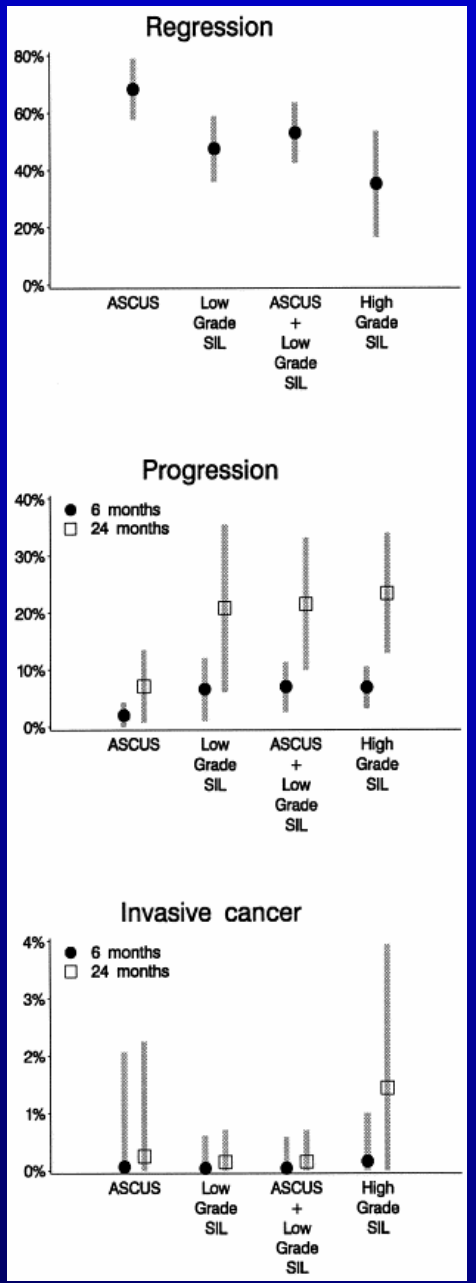
	PATIENTS (N)	REGRESSION (%)	PERSISTENCE (%)	PROGRESSION TO CIS (%)	PROGRESSION TO INVASION (%)
CIN I	4504	57	32	11	1
CIN II	2247	43	35	22	5
CIN III	767	32	<56	-	>12

CIN, cervical intraepithelial neoplasi; CIS, carcinoma in situ

Östör AG : Natural history of cervical intraepithelial neoplasia : A critical review. Int J Gynecol Pathol 12:186, 1993

Pooled estimates with 95% confidence intervals. ASCUS = atypical squamous cells of undetermined significance; SIL = squamous intraepithelial lesion.

Melnikow J et al: Natural history of cervical squamous intraepithelial lesions: A meta-analysis. Obstet Gynecol 1998.



The Bethesda System 2

- Interobserver and intraobserver variability: Lack of reproducibility for the identification of 3 or 4 categories among different laboratories and even by the same cytologist
- Reducing the discordance between interpretation of cytologic and histologic specimens by placing moderate dysplasia (CIN 2), severe dysplasia (CIN 3) and carcinoma in situ into one category (HSIL)

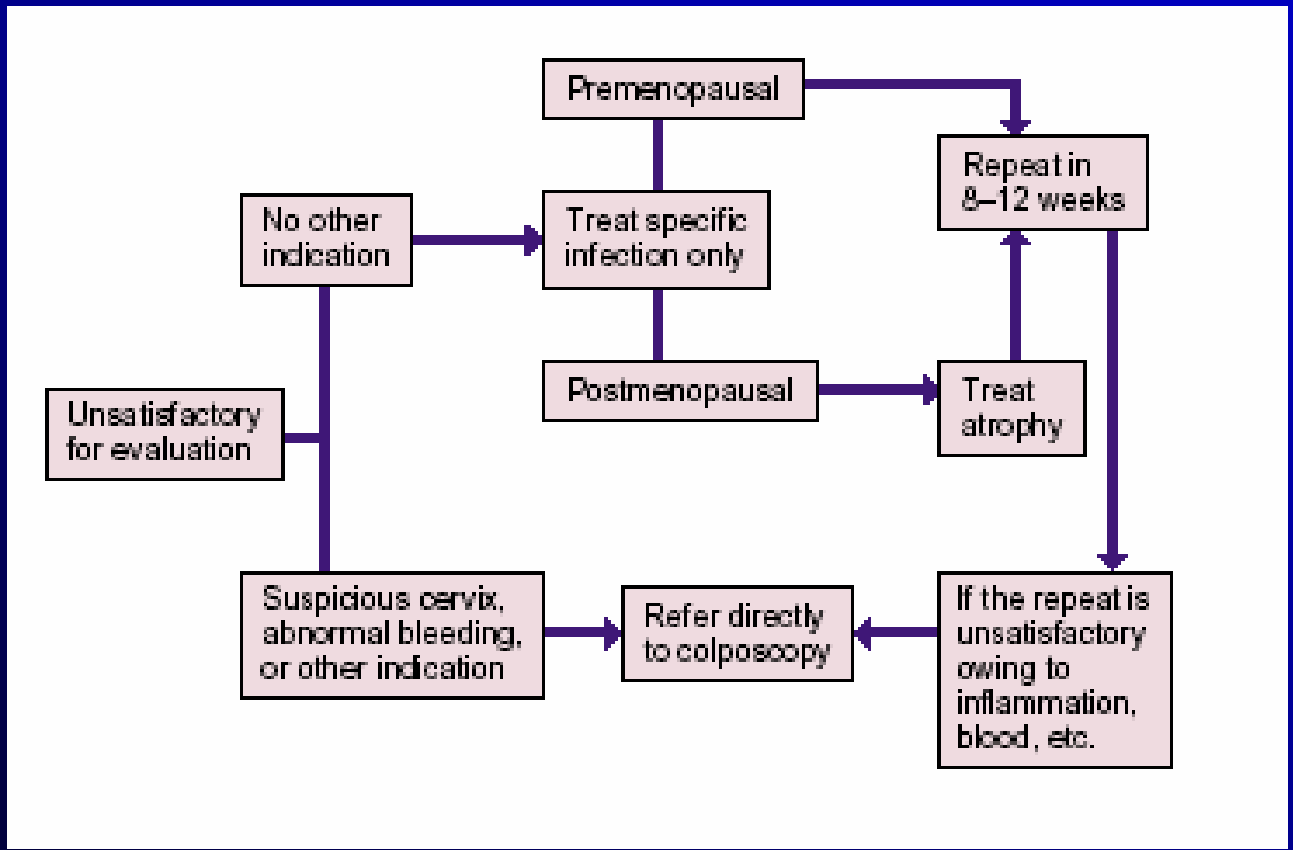
Adequacy of the Specimen: Unsatisfactory Smear

- TBS 2001 separates unsatisfactory for technical reasons from those processed but unsatisfactory
- Typical rates of unsatisfactory smears are reported as 0.5 % (mean 0.95 %)
- The most common reason of for an unsatisfactory smear is scant cellularity, followed by obscuring inflammation and obscuring blood
- A significant number shows SIL/Ca in follow-up

Adequacy of the specimen: endocervical cells

- In TBS 2001 the absence of endocervical cells does not affect specimen adequacy
- Women with smears lacking endocervical cells are not more likely to have squamous lesions on follow up than women with endocervical cells
- No association between false-negative interpretations of smears and lack of endocervical cells
- No relevance if the specimen shows HSIL

Algorithm for follow-up of smears unsatisfactory for evaluation



American Society of Colposcopy and Cervical Pathology

ASCUS

- Atypical Squamous Cells of Undetermined Significance
- Combination of technical and interpretive problems
- Problems of sampling
- Problems of cellular preservation
- Problems of microscopic observation
- Poor interobserver reproducibility

ASCUS/LSIL

- The management of ASCUS/LSIL is of concern because a small but important minority have HSIL or even invasive carcinoma

ASCUS Survey

- Incidence of ASCUS: 3 % - 5 %
- ASCUS associated with HSIL: 15 %
- Almost 50 % of all HSIL is preceded by ASCUS
- HPV DNA testing is the most sensitive test for HSIL (96 % sensitivity)
- Negative predictive value of HPV DNA: 99%

Revision Bethesda 2001: ASCUS

- Bethesda 1991:
  - ASCUS-FR: favoring a reactive process
  - ASCUS-FN: favoring a dsyplastic/neoplastic process
  - ASCUS-NOS: not other specified
- Bethesda 2001:
  - ASC-US: undetermined significance
  - ASC-H: suggestive of HSIL

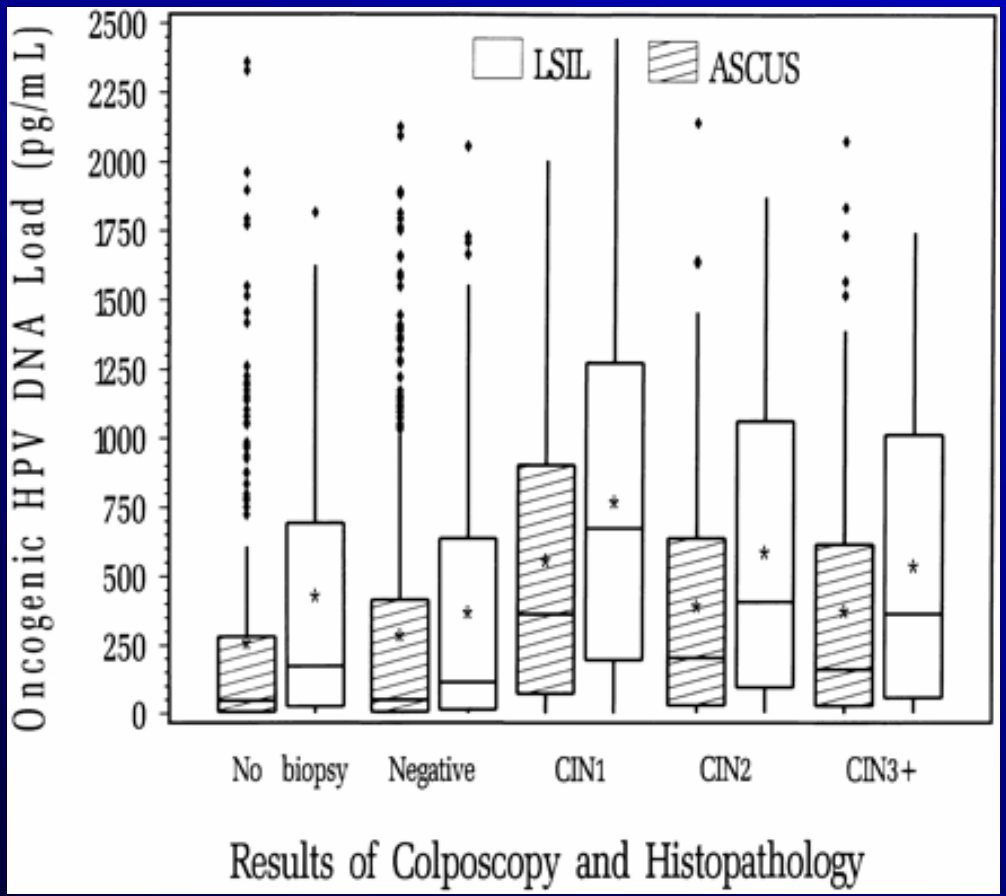
ASC Survey

- ASC-H (Atypical Squamous Cells favoring HSIL)
- ASC-H: 24% - 94% CIN 2, 3 histopathology
- ASC-US: 5% - 10% CIN 2, 3 histopathology

HPV DNA Testing for the Management of ASCUS

Author (No of Patients)	Repeat Cytology Sensitivity (95% CI)	HPV Testing Sensitivity (95% CI)
Ferris1998 (144)	0.70 (0.42-0.98)	0.89 (0.69-1.00)
Manos 1999 (995)	0.76 (0.65-0.87)	0.89 (0.81-0.97)
Bergeron 2000 (111)	0.67 (0.50-1.00)	0.83 (0.62-1.00)
Lin 2000 (74)	NA (not applicable)	1.00
Shlay 2000	NA	0.93 (0.81-1.00)
Salomon 2001	0.85 (0.81-0.89)	0.96 (0.94-0.98)

Human papillomavirus (HPV) load stratified by results of colposcopy and final enrollment histopathology for 2198 women with atypical squamous cells of undetermined significance (ASCUS) and 848 women with low-grade squamous intraepithelial lesion (LSIL) enrolled in the ASCUS/LSIL Triage Study (ALTS). Cervical specimens stored in PreservCyt were tested for the presence of HPV DNA as described previously *(6,7)*. **Striped bars** represent viral load (pg/mL) for women with cervical smears interpreted as ASCUS by a community pathologist **open bars** represent the viral load for women with cervical smears interpreted as LSIL; **upper boundary of the box** represents the 75th percentile; **lower boundary of the box** represents the 25th percentile; **center line in the box** represents the median; **asterisk** represents the mean; **whiskers** represent 1.5x the distance between the 25% and 75% percentiles; and **diamonds** represent outliers. CIN = cervical intraepithelial neoplasia.



Sherman M et al: ASCUS/LSIL Triage Study: J Natl Cancer Inst 2002

ASC-US Management

- ASC-US may be the precursor of HSIL before cancer develops
- HPV tests effectively identifies patients at risk for existent HSIL with an similar efficacy as colposcopy
- Women whose HPV DNA is negative can be similarly managed as negative Pap smears (negative predictive value: 99%)

LSIL Survey

- Incidence of LSIL: 1.6 %
- LSIL associated with HSIL: 18 % (10 % - 70 %)
- 0.3 % inv ca, 68 % CIN 1
- Almost 25 % of all HSIL is preceded by LSIL

LSIL

- LSIL: 85% to 90% are high-risk HPV positive
- LSIL contains both low-risk and high-risk HPV, in contrast to HSIL
- Predominantly made up of productive viral infections (condyloma and CIN 1)
- TBS combines CIN 1 and HPV changes into LSIL

LSIL

- Factors related to the development: young age, presence of high-risk HPV, persistence of HPV infection
- HPV infection reflects sexual activity with an immature transformation zone
- Only 5.1 % of HPV infection and persistence (6 month) during the 3 year study developed SIL, 93 % CIN 1 (Ho GYet al, N Engl J Med 1998)
- Progression rate from LSIL to HSIL: 10 % - 20 %

AGUS, AGC and Cervical Neoplasia

Atypical Glandular Cells (AGC) is associated with a substantially greater risk for cervical neoplasia than Atypical Squamous Cells (ASC) / LSIL

Ronnett et al, Hum Pathol, 1999

Revision Bethesda 2001: AGUS

- Bethesda 1991:
  - AGUS-FR: favoring a reactive process
  - AGUS-FN: favoring a dsyplastic/neoplastic process
  - AGUS-NOS: not otherwise specified
- Bethesda 2001:
  - AGC (endocervical, endometrial) or AGC-NOS (Atypical Glandular Cells not otherwise specified)
  - AGC-FN: Atypical Glandular Cells (endocervical or glandular)
  - Adenocarcinoma in situ (endocervical)

AGC Survey

- AGC (AGUS-FN) and AGC (NOS) was separated by TBS 2001, because they represent women at different risk for neoplasia
- AGC-FN: 27 % - 96 % CIN 2,3; AIS, invas Ca
- AGC-NOS: 9 % - 41 %

AGUS Survey

- Incidence of AGUS: 0.1 % - 0.4 %
- AGUS associated with HSIL: 9 % - 40 %
- AGUS associated with adenoca in situ: 8 %
- associated with endometrial ca: 10 %
- associated with endometrial hyperplasia: 12 %

AGUS, Significant Lesions and Age

Lesions	No of cases (27)	Mean Age
AdenoCa (endometr)	12	63
Hyperplasia (endometr)	3	66
CIN 1	4	47
CIN 2, 3	6	45
Metast Ca	1	61
AIS	1	26

Liu et al, J LGTD, 2002

Methods of Histologic Evaluation

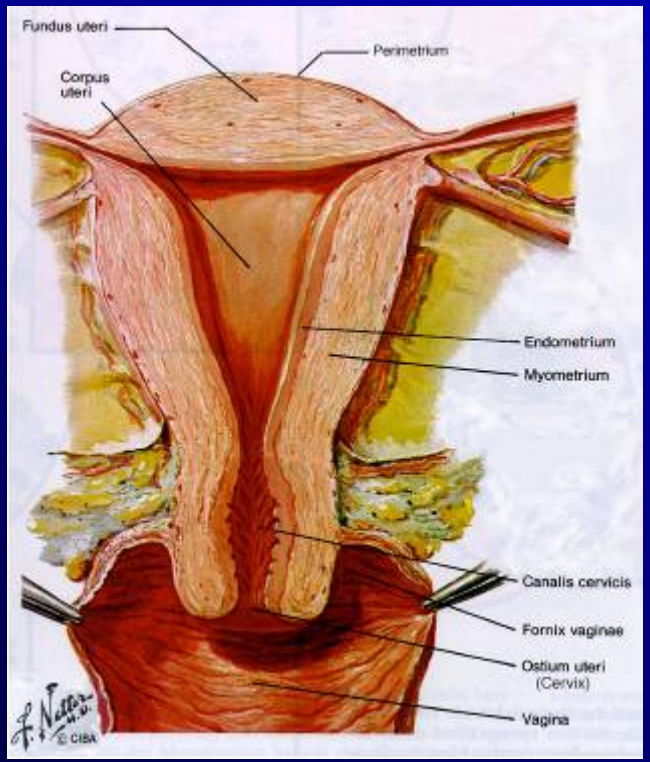
Diagnostic technique	No. of patients (%) (Total : 88)
Endocervical Curettage (ECC)	31 (35.2 %)
Conisation	5 (5.7 %)
Endometrial Curettage (EMC)	15 (17 %)
ECC / EMC	29 (33 %)
Hysterectomy	6 (6.8 %)
Vaginal Biopsy	2 (2.3 %)

Liu W et al, J LGTD 2002

AGUS after hysterectomy

- Because data show that women with glandular cells after hysterectomy rarely developed neoplastic lesions regardless of the history of prior malignancy, TBS 2001 stated that these smears (AGUS) should be called negative
- Origins: prolapse of the fallopian tube, vaginal endometriosis, fistula, vaginal adenosis or metaplasia associated with radiation or chemoth

Management of AGS



FN: endocervical, glandular

Endocervical Curettage

Endometrial Curettage

NOS

AGS

AGC: NOS and FN

- AGC (FN) who do not have cervical neoplasia detected continue to be at risk, management with repeat cervical cytology is unacceptable
- AGC NOS have been found to be at relative low risk for a missed lesion (Veljovich, 1998): repeat cytology (until 4 consecutive negative results)
- Persistent AGC-NOS, AGC-FN or AIS have been found to be high risk: cold-knife conisation

AGC or AIS and Endometrial sampling

- AGC glandular (atypical endometrial cells)
- In all women older than 35
- In women younger than 35 who have unexpected vaginal bleeding

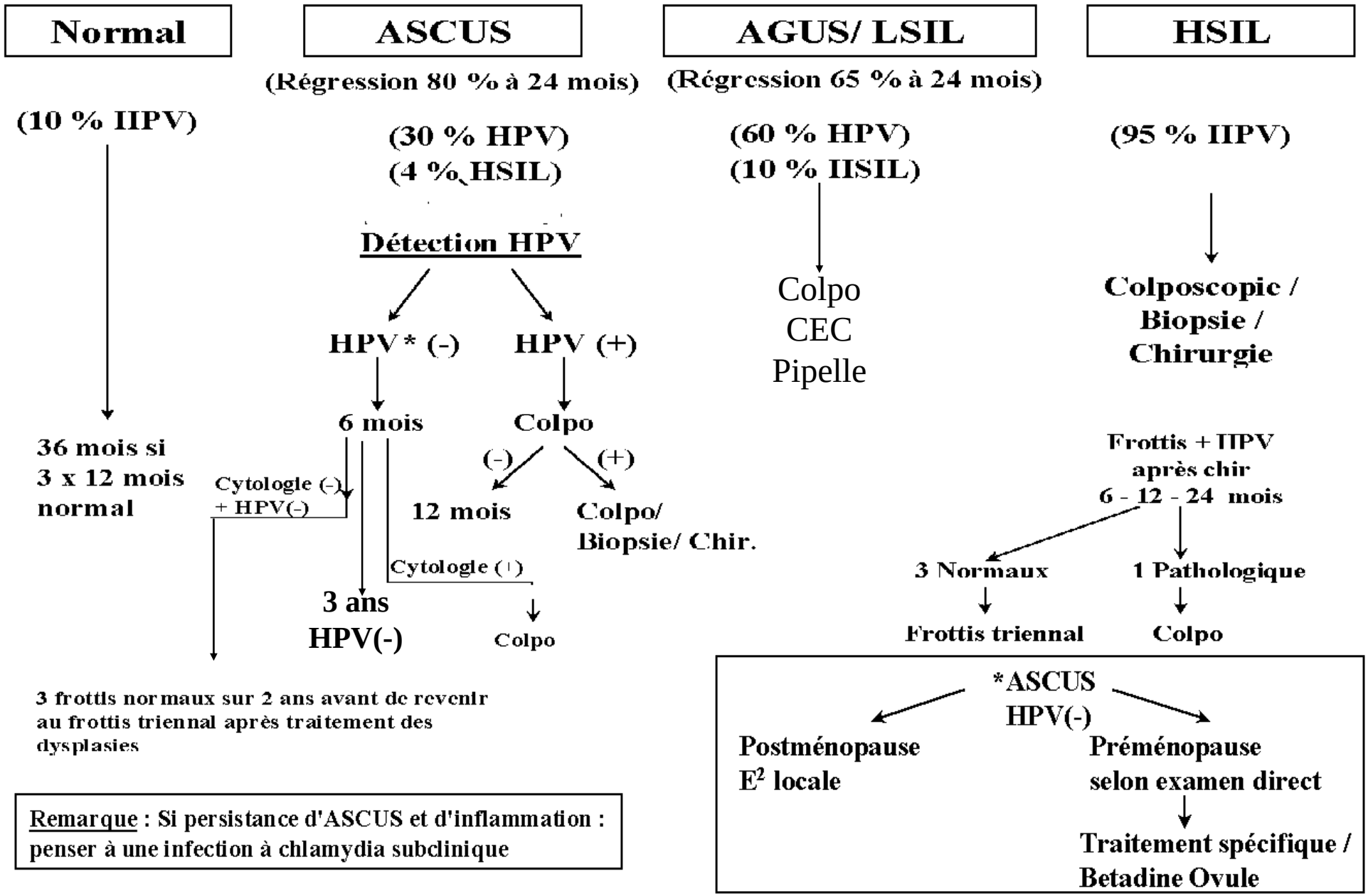
Adenocarcinoma in situ (AIS)

- TBS 2001concluded that the criteria for adenocarcinoma in situ have been shown to be predictive and reproducible that a separate category be established
- AIS (cytol) is associated with AIS (histopath) in 48 % - 69 % or invasive cervical adenoca in 38 %
- 50 % have coexisting squamous abnormality

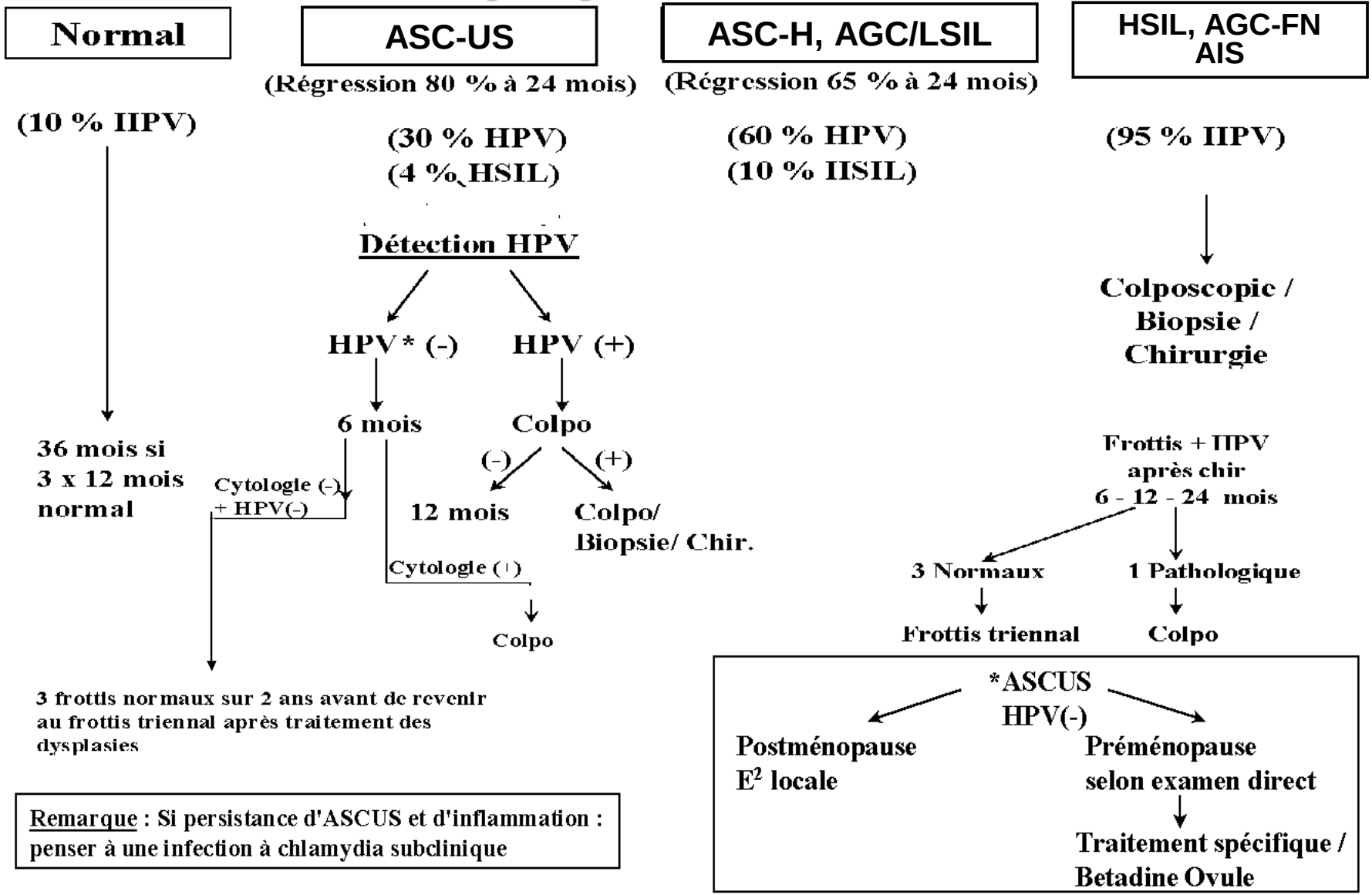
AGC and AIS or Adenoca

- Many cases of biopsy-confirmed AIS had no observed colposcopic abnormalities, and even combinations with cytology can miss small endocervic adenoca and AIS (Cullimore J, 1992)
- Endocervical sampling can detect glandular neoplasia that is missed by colposcopy

Dépistage du cancer du col



Dépistage du cancer du col



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Conclusion (Bethesda System 2001)

- Atypical Squamous Cells (ASC) is subcategorised in ASC-US (undetermined significance) and in ASC-H (suggestive of HSIL)
- ASC-US should be managed using by one of following program:
  - cytology follow-up
  - Immediate colposcopy
  - High-risk HPV DNA testing
- HPV DNA testing is the preferred approach with liquid-based cyto
- No role for HPV testing in LSIL
- ASC-H, LSIL, HSIL and AGUS should be referred for immediate colposcopy
- ASC-US with oncogenic HPV types are equated to LSIL