Management of Abnormal Cervical Cytology and Histology

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 Universally accepted guideline for management of cytologic and histologic abnormalities doesn’t exist.
Cervical cancer screening

- Cytology based
  - European Guideline

- Co-testing (cytology and hrHPV DNA)
  - ASCCP Guideline

- Primary HPV screening
  - Turkish National Screening Program
New approaches

- hrHPC DNA typing
- HPV 16 and HPV 18 subtyping
- p16 immunostaining of CIN2 for histologic specimen
  - Really CIN2 exist or represent a mixture of CIN1 and CIN3
Primary HPV Screening

Fig. 1. Recommended primary HPV screening algorithm.
Colposcopy after Pap smear
EU Guideline

- Cytologic abnormalities
  - Cut-off ≥ASCUS or ≥LSIL

- Primary HPV screening
  - HPV 16 or 18
  - hrHPV+ and ≥ASCUS
Colposcopy after Pap smear
ASCCP Guideline

- HPV+ ASC-US
- LSIL
- ASC-H
- HSIL
  - 70-75% CIN2-3 in colposcopic biopsy or excisional specimen
- AGC

- “Immediate colposcopy for ASC-US is no more an option”
Different subgroups for management
ASCCP Guideline

- 21-24 y. women
- 30-64 y. women
- ≥65 y. women
- Pregnant women
- Postmenopausal women
- Screened adolescent according to 21-24 y. group
Negative cytology and positive HPV test

Management of Women ≥ Age 30, who are Cytology Negative, but HPV Positive

Repeat Cotesting
@ 1 year
Acceptable

HPV DNA Typing
Acceptable

Cytology Negative and HPV Negative

≥ASC or HPV positive

HPV 16 or 18 Positive

HPV 16 and 18 Negative

Repeat Cotesting
@ 3 years

Colposcopy

Manage per ASCCP Guideline

Manage per ASCCP Guideline

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Management of Women with Atypical Squamous Cells of Undetermined Significance (ASC-US) on Cytology

- **Repeat Cytology**
  - @ 1 year
  - Acceptable
  - Negative
  - ≥ ASC
    - Routine Screening
    - (Cytology in 3 years)

- **HPV Testing**
  - Preferred
  - HPV Positive
    - (managed the same as women with LSIL)
  - HPV Negative
    - Repeat Cotesting
    - @ 3 years

- **Colposcopy**
  - Endocervical sampling preferred in women with no lesions, and those with inadequate colposcopy; it is acceptable for others

- **Manage per ASCCP Guideline**

*Management options may vary if the woman is pregnant or ages 21-24.*
ASC-US or LSIL (21-24 years group)

Management of Women Ages 21-24 years with either Atypical Squamous Cells of Undetermined Significance (ASC-US) or Low-grade Squamous Intraepithelial Lesion (LSIL)

Women ages 21-24 years with ASC-US or LSIL

Repeat Cytology @ 12 months Preferred

HPV Positive

Reflex HPV Testing
Acceptable for ASC-US only

HPV Negative

Routine Screening

Negative, ASC-US or LSIL

ASC-H, AGC, HSIL

Repeat Cytology @ 12 months

Negative x 2 ≥ ASC

Routine Screening

Colposcopy

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77% HPV infection

In ALTS study LSIL natural history approaches to HPV+ ASCUS

Similar management possible

>30 y. HPV neg-LSIL women

- KPNC data: CIN3+ risk as low as ASCUS
Management of Women with Low-grade Squamous Intraepithelial Lesions (LSIL)*

**LSIL with negative HPV test**
- Preferred
- Repeat Cotesting @ 1 year
- Cytology Negative and HPV Negative
  - Repeat Cotesting @ 3 years

**LSIL with no HPV test**
- Acceptable
- Colposcopy
  - ≥ASC or HPV positive
  - Non-pregnant and no lesion identified
  - Inadequate colposcopic examination
  - Adequate colposcopy and lesion identified
  - Endocervical sampling “preferred”
  - Endocervical sampling “acceptable”

**LSIL with positive HPV test**
- CIN2,3
  - Manage per ASCCP Guideline

**No CIN2,3**
- Manage per ASCCP Guideline

* Management options may vary if the woman is pregnant or ages 21-24 years.
LSIL in pregnancy

Management of Pregnant Women with Low-grade Squamous Intraepithelial Lesion (LSIL)

Pregnant Women with LSIL

Colposcopy
Preferred

No CIN2,3

CIN2,3

Postpartum follow-up

Manage per ASCCP Guideline

Defer Colposcopy
(Until at least 6 weeks postpartum)

^ In women with no cytological, histological, or colposcopically suspected CIN2,3 or cancer

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Management of Women with Atypical Squamous Cells: Cannot Exclude High-grade SIL (ASC-H)*

Colposcopy
Regardless of HPV status

No CIN2,3

Manage per ASCCP Guideline

CIN2,3

Manage per ASCCP Guideline

*Management options may vary if the woman is pregnant or ages 21-24 years.
ASC-H and HSIL (21-24 years group)

Management of Women Ages 21-24 yrs with Atypical Squamous Cells, Cannot Rule Out High Grade SIL (ASC-H) and High-grade Squamous Intraepithelial Lesion (HSIL)

Colposcopy
(Immediate loop electrosurgical excision is unacceptable)

No CIN2,3

- Two Consecutive Cytology Negative Results and No High-grade Colposcopic Abnormality
  - Observation with colposcopy & cytology * @ 9 month intervals for up to 2 years
  - Other results
      - Manage per ASCCP Guideline

CIN2,3

- High-grade colposcopic lesion or HSIL Persists for 1 year
  - Biopsy
    - CIN2,3 (if NO CIN2,3, continue observation)
      - Manage per ASCCP Guideline for young woman with CIN2,3

Diagnostic Excisional Procedure

*If colposcopy is adequate and endocervical sampling is negative. Otherwise a diagnostic excisional procedure is indicated.

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HSIL

- Risk relatively high
- 60% CIN2+
- Risk increase with age
- >30 y. 5 year cancer risk 8%
- KPNC data at 5 year
  - CIN3+ 50% and cancer 7%
Management of Women with High-grade Squamous Intraepithelial Lesions (HSIL)*

Immediate Loop Electrosurgical Excision *  
Or  
Colposcopy (with endocervical assessment)

No CIN2,3  
CIN2,3

Manage per ASCCP Guideline

* Management options may vary if the woman is pregnant or ages 21-24.  
* Not if patient is pregnant or ages 21-24.
AGC, cytological AIS and benign glandular changes

- AGC cytology more frequent in squamous lesions
- 50% CIN in AIS cases
- Endometrial cancer
  - HPV test is useless
  - Probability high in older and high risk young women
AGC
Initial work-up

Initial Workup of Women with Atypical Glandular Cells (AGC)

All subcategories (except atypical endometrial cells) → Colposcopy (with endocervical sampling) and Endometrial sampling (if ≥ 35 yrs or at risk for endometrial neoplasia *) → Atypical Endometrial Cells

Atypical Endometrial Cells → Endometrial and Endocervical Sampling

Endometrial and Endocervical Sampling → No Endometrial Pathology → Colposcopy

* Includes unexplained vaginal bleeding or conditions suggesting chronic anovulation.
Subsequent Management of Women with Atypical Glandular Cells (AGC)

- **Initial Cytology is AGC - NOS**
  - No CIN2+, AIS or Cancer:
    - Cotest at 12 & 24 months
    - Both negative: Cotest 3 years later
    - Any abnormality: Colposcopy
  - CIN2+ but no Glandular Neoplasia:
    - Manage per ASCCP Guideline

- **Initial Cytology is AGC (favor neoplasia) or AIS**
  - No Invasive Disease:
    - Diagnostic Excisional Procedure +

+ Should provide an intact specimen with interpretable margins. Concomitant endocervical sampling is preferred.

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Management of abnormal histology
## CIN natural history

### Cervical cancer precursors

<table>
<thead>
<tr>
<th>CIN grade</th>
<th>Regression %</th>
<th>Persistence %</th>
<th>Progression to CIN3 %</th>
<th>Progression to invasive cancer %</th>
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</thead>
<tbody>
<tr>
<td>CIN1</td>
<td>57</td>
<td>32</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>CIN2</td>
<td>43</td>
<td>35</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>CIN3</td>
<td></td>
<td>56</td>
<td></td>
<td>12</td>
</tr>
</tbody>
</table>
Transformation zone types

Type I
- Completely ectocervical
- Fully visible
- Small or large ectocervical component

Type II
- Has an endocervical component
- Fully visible
- May have ectocervical component, which may be small or large

Type III
- Has an endocervical component
- Not fully visible
- May have ectocervical component, which may be small or large
Management of CIN1 (European Guideline)

- **Satisfactory colposcopy**
  - Two options can be recommended
    - Follow-up (cytology at 12 and 24 m or hrHPV DNA at 12m)
    - or treatment (recurrent CIN1)

- **Unsatisfactory colposcopy**
  - Excisional treatment (occult high-grade disease)
Unacceptable treatment for CIN1

- See and treat
- Local destruction procedure in unsatisfactory colposcopy
- Hysterectomy as a primary treatment
Management of CIN2-3 (European Guideline)

- Treatment is necessary
- Excision is preferred
- Recurrence or unsatisfactory colposcopy LLETZ or cold knife conisation
Follow-up after treatment of CIN

- Regular follow-up required

- Frequency and duration of follow-up related to
  - Age: ≥40 persistence or recurrence ↑
  - Type of lesion: glandular lesion
  - Grade: high-grade
  - Histology of excised margin (incomplete excision)
Follow-up after treatment of CIN

- **High-grade (CIN2, CIN3, CGIN)**
  - 6, 12 and 24 m cytology
  - Annually for 5 years
  - Routine screening interval

- **Low-grade**
  - 6, 12 and 24 m cytology
  - Routine screening interval

- Most persistence/recurrence in 24 m
Significance of involved margin

- Negative excision margin associated with lower risk of residual disease

- Endocervical margin involvement associated with higher risk than ectocervical margin

- ≥40 y, risk of persistence/recurrence ↑
Management in other clinical situations
EU Guideline

- Pregnant women
- Adolescent women
- Post-menopausal women
- Hysterectomised women
- Immunocompromised women
- Discrepancy between cytology, colposcopy and histology
No lesion or CIN1 (lesser abnormalities)

**Management of Women with No Lesion or Biopsy-confirmed Cervical Intraepithelial Neoplasia - Grade 1 (CIN1) Preceded by “Lesser Abnormalities”**

- Follow-up without Treatment
  - Cotesting at 12 months
    - HPV (-) and Cytology Negative
      - Age appropriate retesting 3 years later
        - Cytology negative +/- HPV (-)
        - Routine screening
  - ≥ ASC or HPV (+)
    - Colposcopy
      - No CIN
        - CIN2,3
        - CIN1
          - If persists for at least 2 years
            - Follow-up or Treatment

*“Lesser abnormalities” include ASC-US or LSL Cytology, HPV 16+ or 15+, and persistent HPV
**Management options may vary if the woman is pregnant or ages 21-24.
***Cytology if age <30 years, cotesting if age ≥30 years
† Either ablative or excisional methods. Excision preferred if colposcopy inadequate, CIN2+ on ECC, or previously treated.

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No lesion or CIN1 (ASC-H or HSIL)

Management of Women with No Lesion or Biopsy-confirmed Cervical Intraepithelial Neoplasia - Grade 1 (CIN1) Preceded by ASC-H or HSIL Cytology

- **Cotesting** at 12 and 24 months *
  - **HPV(-) and Cytology Negative at both visits** → **Colposcopy**
  - **HPV(+) or Any cytology abnormality except HSIL**
    - **Age-specific retesting in 3 years+**
  - **HSIL at either visit**

- **Diagnostic Excision Procedure**

- **Review of cytological, histological, and colposcopic findings** → **Manage per ASCCP Guideline for revised diagnosis**

*Provided colposcopy is adequate and endocervical sampling is negative

^Except in special populations (may include pregnant women and those ages 21-24)

+Cytology if age <30 years, cotesting if age ≥30 years
No lesion or CIN1 (21-24 years group)

Management of Women with No lesion or Biopsy-confirmed Cervical Intraepithelial Neoplasia - Grade 1 (CIN1) in Women Ages 21-24

After ASC-US or LSIL

- Repeat Cytology @ 12 months

- < ASC-H or HSIL
  - Repeat Cytology @ 12 mos
  - Negative
    - Routine Screening
  - ≥ ASC
    - Colposcopy

- ≥ ASC-H or HSIL
  - Inadequate colposcopy
  - All three approaches are acceptable

After ASC-H or HSIL

- Inadequate colposcopy
  - Diagnostic Excisional Procedure *
  - HSIL @ other visit
  - Routine Screening
  - Manage per ASCCP Guideline

- Adequate colposcopy
  - Observation with colposcopy & cytology @ 6 mo intervals for 1 year
  - Negative cytology @ both visits
  - Other results

* Not if patient is pregnant
^ Includes referral cytology, colposcopic findings, and all biopsies

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Biopsy-confirmed CIN2 and 3

Management of Women with Biopsy-confirmed Cervical Intraepithelial Neoplasia - Grade 2 and 3 (CIN2,3) *

Adequate Colposcopy

Inadequate Colposcopy or Recurrent CIN2,3 or Endocervical sampling is CIN2,3

Either Excision† or Ablation of T-zone *

Diagnostic Excisional Procedure †

Cotesting at 12 and 24 months

Any test abnormal

2x Negative Results

Repeat cotesting in 3 years

Routine screening

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*Management options will vary in special circumstances or if the woman is pregnant or ages 21-24
†If CIN2,3 is identified at the margins of an excisional procedure or post-procedure ECC, cytology and ECC at 4-6mo is preferred, but re-excision is acceptable and hysterectomy is acceptable if re-excision is not feasible.
Biopsy-confirmed CIN2 and 3 in young women

Management of Young Women with Biopsy-confirmed Cervical Intraepithelial Neoplasia - Grade 2,3 (CIN2,3) in Special Circumstances

**Young Women with CIN2,3**

Either treatment or observation is acceptable, provided colposcopy is adequate. When CIN2 is specified, observation is preferred. When CIN3 is specified, or colposcopy is inadequate, treatment is preferred.

**Observation - Colposcopy & Cytology**

- @ 6 month intervals for 12 months
  - 2x Cytology Negative and Normal Colposcopy
    - Cytology in 1 year → Either test abnormal
    - Both tests negative
      - Cytology in 3 years
  - Colposcopy worsens or High-grade Cytology or Colposcopy persists for 1 year

**Treatment using Excision or Ablation of T-zone**

- CIN3 or CIN2,3 persists for 24 months
  - Treatment Recommended

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AIS management

Management of Women Diagnosed with Adenocarcinoma in-situ (AIS) during a Diagnostic Excisional Procedure

**Hysterectomy - Preferred**

**Conservative Management**
Acceptable if future fertility desired

- Margins Involved or ECC Positive
  - Re-excision Recommended
- Margins Negative
  - Re-evaluation*
  - 6 months - acceptable

Long-term Follow-up

* Using a combination of cotesting and colposcopy with endocervical sampling

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Treatment modalities

- Office based
- Cheap
- Fast
- Minimal or no discomfort
- Curative
- Few or no side effect (bleeding, discomfort, stenosis)
- Must provide sufficient cytologic follow-up
Treatment modalities

- Ablative
  - Cryotherapy
  - Electrocoagulation diathermy
  - Cold coagulation
  - CO₂ laser ablation

- Excisional
  - Diathermy loop excision
  - Laser cone biopsy
  - Cold conisation
  - Hysterectomy