Hodnocení cervikální cytologie

The Bethesda system 2014

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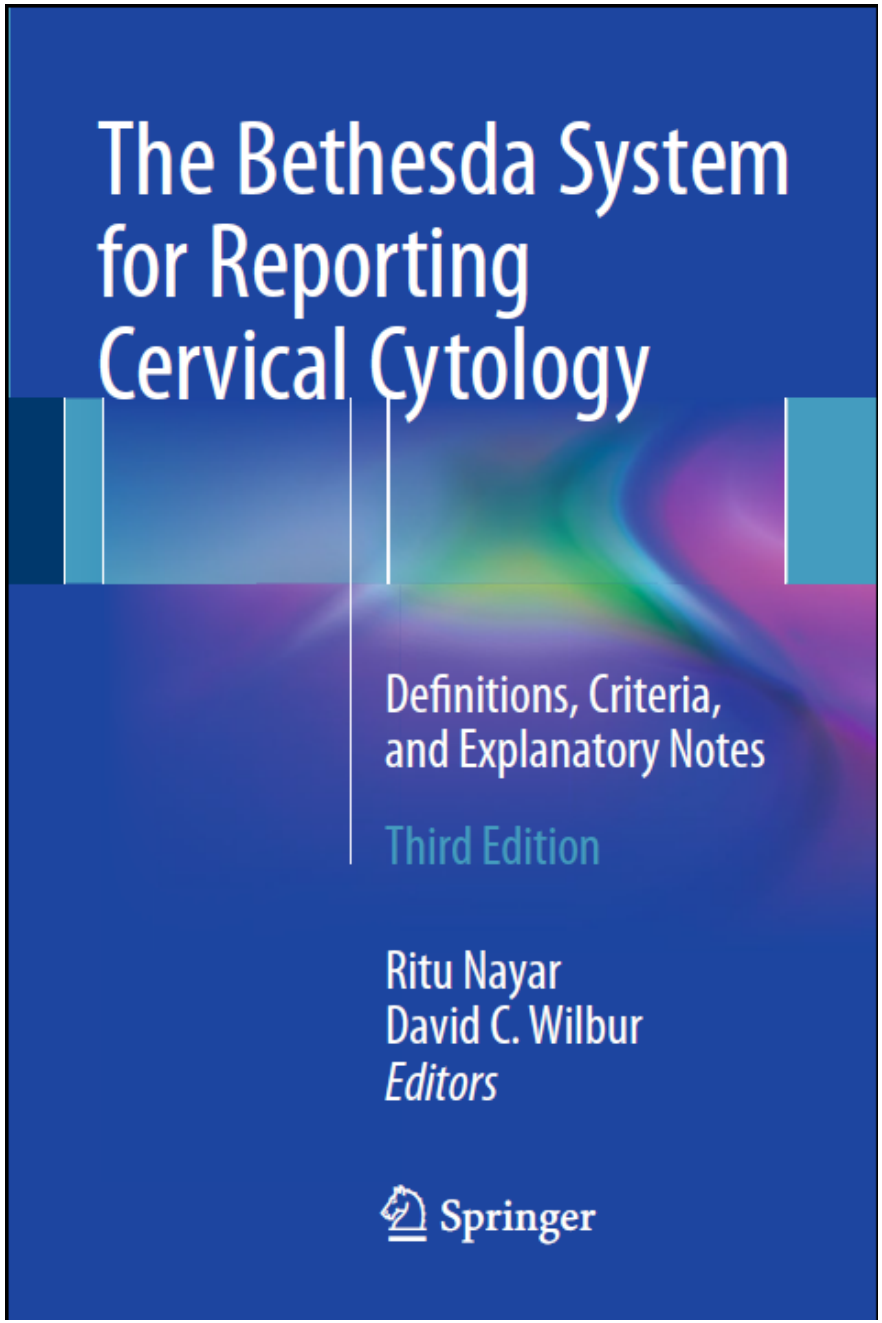
XXIV. Cytologický den Praha



Terminologie musí být:

1. **Výstižná a poskytovat klinicky relevantní informace**
2. **Uniformní a reprodukovatelná bez ohledu na místní zvyklosti laboratoří kdekoliv na světě**
3. **odrážet současné poznatky o neoplaziích děložního čípku**

1988 2-stupňový systém SIL

Historie

1991 **1. workshop - terminologická kriteria, adekvátnost vzorku**

1994 **1. Bethesda atlas**

2001 **2. workshop - využití internetu - spolupráce > 400 cytopatologů > 25 zemí**

2004 **2. Bethesda atlas - rozvoj LBC - specifická kriteria (*ThinPrep, SurePath*), ↑ fotodokumentace**

Bethesda terminologie - *štítná žláza, pankreas, moč*

Bethesda 2014 - proč? - změny

- v prevenci - HPV vakcinace
- ve skríningu - cotesting Pap + HPV
  - primární HPV skríning
- v managementu
- nová histopatologická terminologie WHO 2014

Adekvátnost vzorku

- **správné provedení stěru**
- **uspokojivý** x **neuspokojivý**
- **nejčastěji nízká buněčnost, > 75% překrytí bb. - krev, zánět**
- **nález atypických bb. - stěr vždy uspokojivý**
- **dlouhodobé studie - neuspokojivé stěry mají ↑riziko SIL, zejména HR HPV +**
- **neuspokojivý stěr - opakovat 3-4 měs., 2x po sobě → kolposkopie**

Fig. 1.12 Squamous cellularity: this image depicts the appearance of a 4× field of a conventional preparation with approximately 75 cells. The specimen is unsatisfactory if all fields have this level, or less, of cellularity. It is to be used as a guide in assessing the squamous cellularity of a conventional smear (Used with permission, © George Birdsong, 2003)

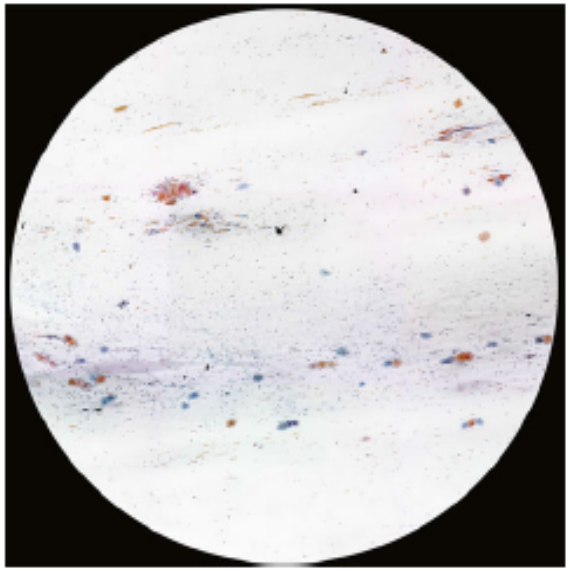
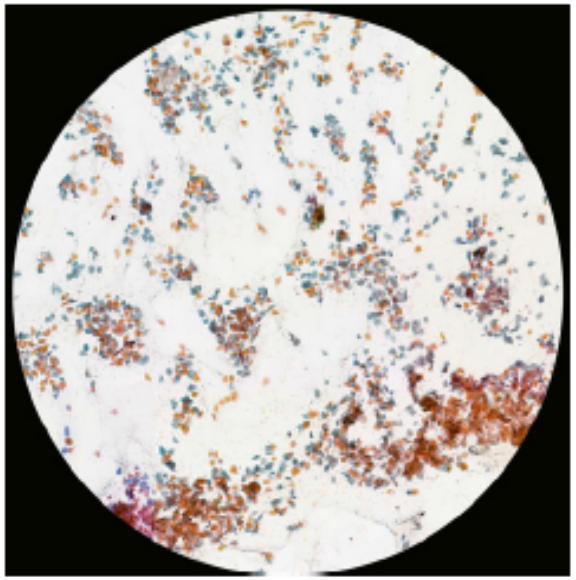


Fig. 1.16 Squamous cellularity: this image depicts the appearance of a 4× field of a conventional preparation with approximately 1,400 cells. A minimum of six fields with similar (or greater) cellularity are needed to call the specimen adequate (Used with permission, © George Birdsong, 2003)



- **referenční obrázky**
- **modifikace - radiace , chemoterapie, hysterektomie, trachelektomie = atrofie, reparativní změny, stenosy, alterovaná anatomie - i 2 000 bb. - *ANAMNÉZA!***

EC/TZ komponenta

- není určující pro adekvátnost vzorku
- popsána přítomnost či absence (kvalita stěru)
- minimum 10 dobře zachovalých endocervikálních nebo metaplastických bb. x atrofie, laktace, gestageny
- význam absence - kontroverzní
- není třeba zkracovat skríningový interval
- anamnesticky AGC, AIS

NILM

Normal Cellular Elements
- Squamous cells
- Endocervical cells
- Endometrial cells
- Lower uterine segment cells

Nonneoplastic Findings (Optional to Report)
- Nonneoplastic cellular variations
  - Squamous metaplasia
  - Keratotic changes
  - Tubal metaplasia
  - Atrophy
  - Pregnancy-associated changes
- Reactive cellular changes associated with:
  - Inflammation (includes typical repair)
  - Lymphocytic (follicular) cervicitis
  - Radiation
  - Intrauterine contraceptive device (IUD)
- Glandular cells status post hysterectomy

Organisms
- *Trichomonas vaginalis*
- Fungal organisms morphologically consistent with *Candida* spp.
- Shift in flora suggestive of bacterial vaginosis
- Bacteria morphologically consistent with *Actinomyces* spp.
- Cellular changes consistent with herpes simplex virus
- Cellular changes consistent with cytomegalovirus

Tubální metaplázie

Fig. 2.21 Tubal metaplasia (*CP*). Ciliated columnar endocervical cells. A goblet cell is seen at the center with its nucleus closer to the top of the image (*arrow*)

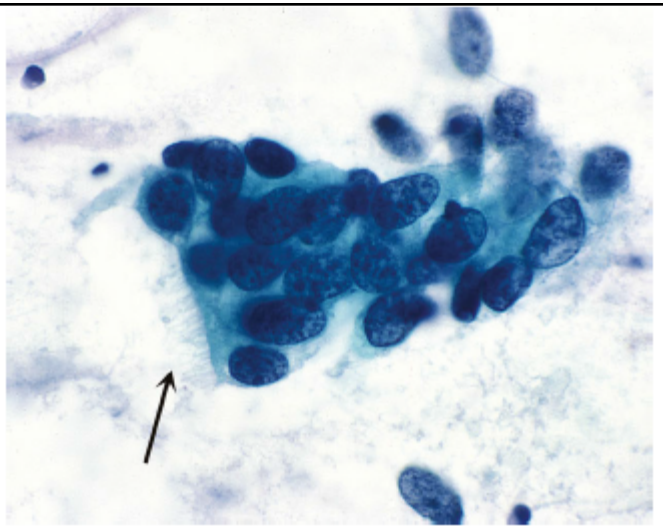
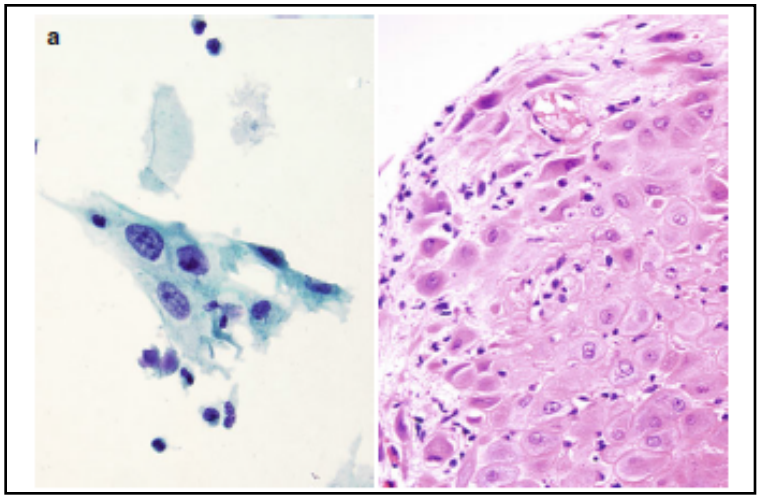


Fig. 2.19 Tubal metaplasia (*CP*). Ciliated cells derived from tubal metaplasia. Note terminal bar and cilia at left edge (*arrow*). Tubal metaplasia shows prominent pseudostratification and can have enlarged nuclei that make it a look-alike for endocervical adenocarcinoma in situ

Těhotenské změny



Deciduální bb. - změny stromatu → ASCUS, LSIL

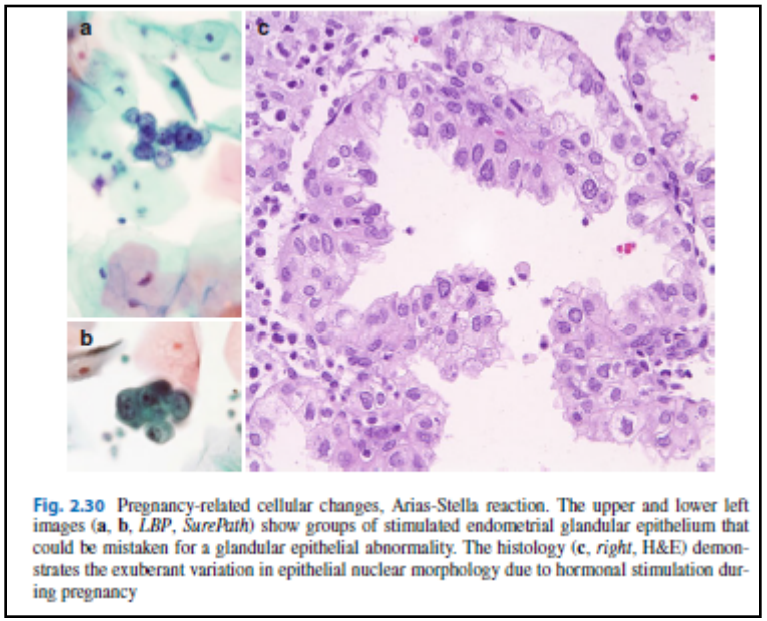


Fig. 2.30 Pregnancy-related cellular changes, Arias-Stella reaction. The upper and lower left images (**a**, **b**, *LBP*, *SurePath*) show groups of stimulated endometrial glandular epithelium that could be mistaken for a glandular epithelial abnormality. The histology (**c**, *right*, H&E) demonstrates the exuberant variation in epithelial nuclear morphology due to hormonal stimulation during pregnancy

Arias-Stella reakce - změny žlazových bb.

IUD změny

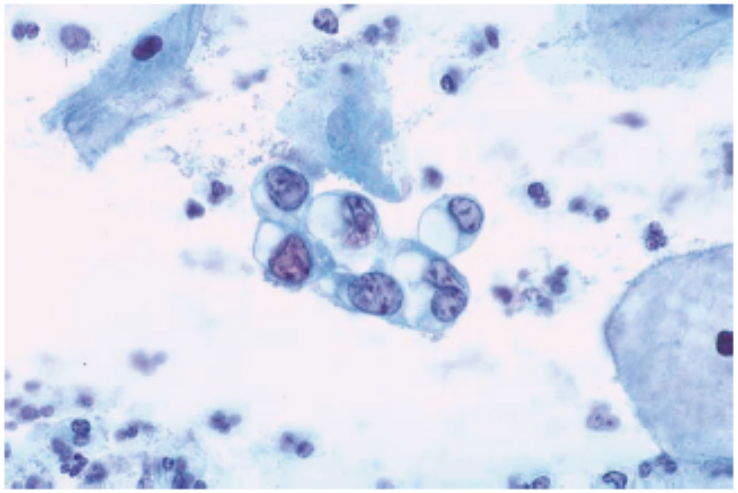


Fig. 2.45 Reactive-reparative cellular changes: IUD (*CP*). Reactive cellular changes associated with intrauterine contraceptive device (IUD). Note small cluster of glandular cells with cytoplasmic vacuoles displacing nuclei

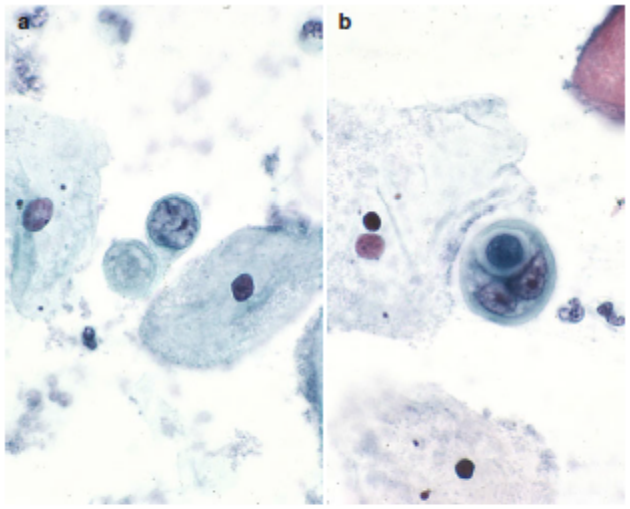


Fig. 2.47 Reactive-reparative cellular changes: IUD (*CP*). Epithelial cells with a high nuclear to cytoplasmic ratio may mimic high-grade squamous intraepithelial lesion (HSIL) (*left*, **a**); however, the morphologic spectrum of abnormalities usually present with squamous intraepithelial lesions is absent. Presence of nucleoli in isolated cells with a high N/C ratio as seen in this cell (*right*, **b**) is not typical of HSIL. Obtaining a history of the presence of an IUD is important in the face of this type of abnormal morphology

Malé nezralé bb., vakuolizace cytoplazmy - pečetní prsten, ↑N/C poměru→ HSIL/ASC-H, 3D klastry - mimikr adenokarcinomu , změny přetrvávají i měsíce po odstranění IUD, HPV test

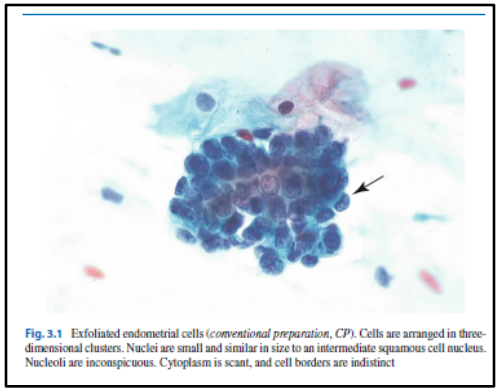


Fig. 3.1 Exfoliated endometrial cells (*conventional preparation, CP*). Cells are arranged in three-dimensional clusters. Nuclei are small and similar in size to an intermediate squamous cell nucleus. Nucleoli are inconspicuous. Cytoplasm is scant, and cell borders are indistinct

The Bethesda system

- **1991 - odloučené endometrální buňky u postmenopauzálních žen jako epiteliální abnormita**

  (prediktivní hodnota pro ca endometria 6 %)

- **2001 - popis u žen nad 40 let věku, nejedná se o abnormitu**

  (prediktivní hodnota pro ca endometria 1 %)

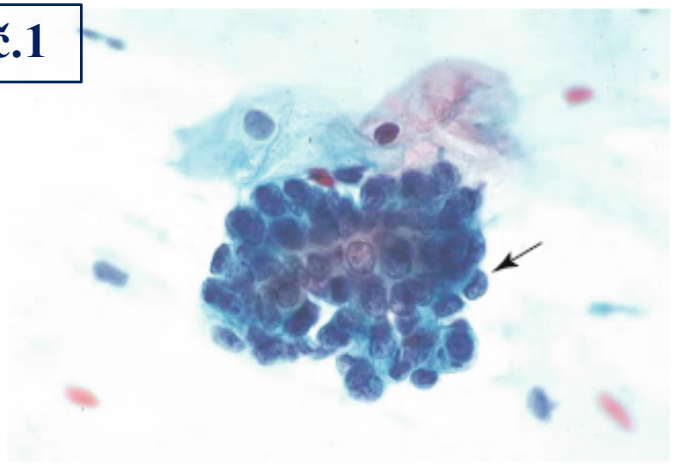
Nově - popis endometrálních bb.

- **odloučené** *(exfoliované)* **endometrální buňky nad 45 let**

exfoliované x abradované endometrální bb.

- **u známé PM - koreluje s menstruačním cyklem**
- **souvislost - benigní endometrium, hormonální změny, méně často závažná patologie endometria**
- **postmenopauzální /symptomatické ženy - klinická korelace vyšetření endometria**

č.1



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č.2

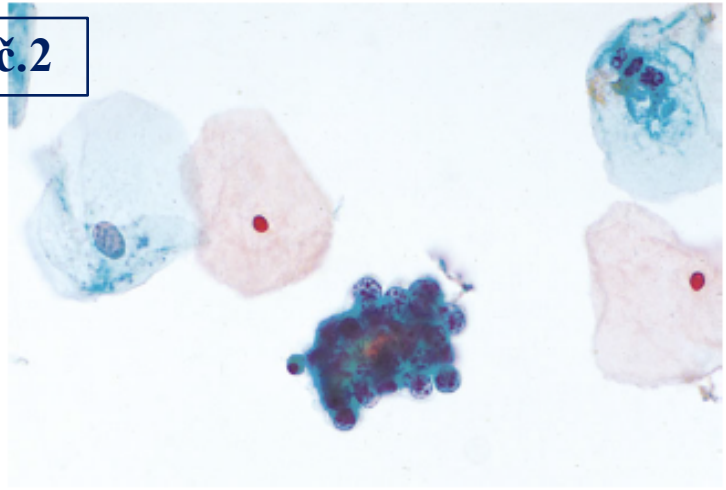


Fig. 3.2 Exfoliated endometrial cells (liquid-based preparation (*LBP*), *ThinPrep*)

č.3

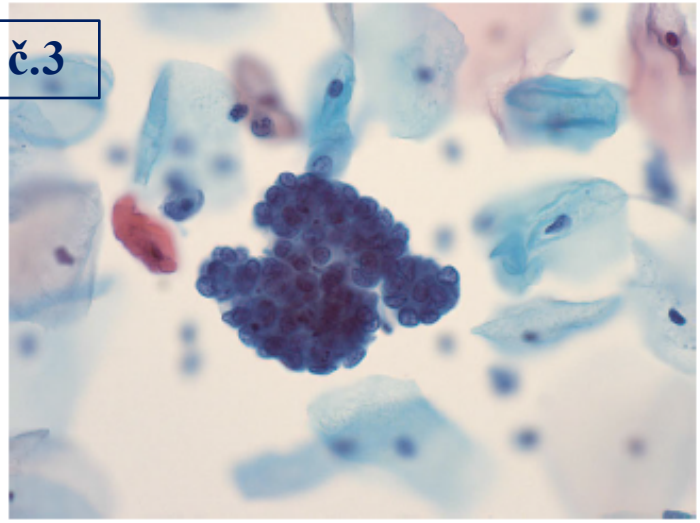


Fig. 2.5 Endometrial cells (*LBP, SurePath*). A tight cluster of endometrial glandular cells with nuclei having cross-sectional areas slightly smaller than the 35 μm² of intermediate cells. Endometrial cell nuclear to cytoplasmic ratios are high and the cells tend to form three-dimensional groups. The small and monotonous nuclear size should prevent overinterpretation as a squamous, or glandular abnormality

Exfoliované endometriální bb.

č.1 - conventional preparation, *CP*

č.2 - liquid-based preparation, *ThinPrep*

č.3 - liquid-based peparation, *SurePath*

Abradované endometrální bb.

- endometrium a dolní děložní segment (DDS, LUS)
- nesouvisí se ↑ rizikem endometrálního Ca
- není třeba popisovat
- po excizních výkonech na čípku
- bifazické - stromální + žlazová komponenta
- mimikr AGC

Dolní děložní segment

ASC - atypical squamous cells

- nejčastější závěr abnormální cytologie
- cytologické změny naznačují SIL, ale kvalitativně či kvantitativně nesplňují definiční kriteria
- heterogenní skupina - HPV inf., SIL, zánět, atrofie s degenerací, hormonální změny, artefakty
- USA - 40-50% ASC má HR HPV +

ASC-

→ US „undetermined significance“

→ H „high-grade squamous intraepithelial lesion cannot be excluded“

ASC-US

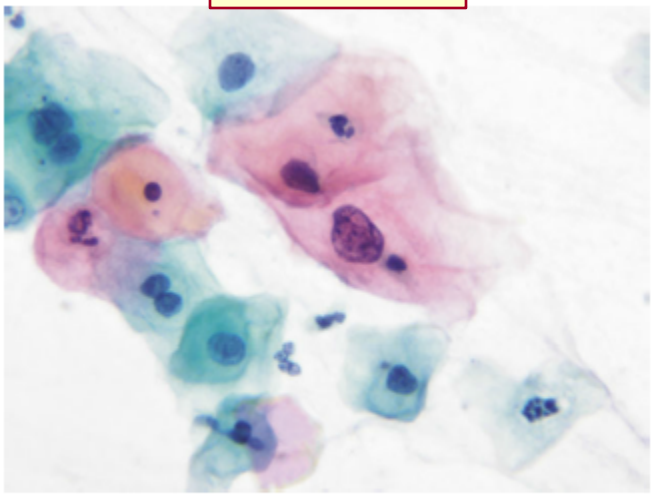


Fig. 4.9 ASC-US (*LBP, ThinPrep*). A 25-year-old woman. Intermediate cells with nuclear enlargement ×2–3 that of normal intermediate squamous cell nucleus. There are rare binucleated cells. Slight nuclear irregularity and hyperchromasia are present that do not meet the diagnostic criteria for LSIL. A repeat cervical cytology showed similar findings. Follow-up biopsy revealed LSIL (CIN1)

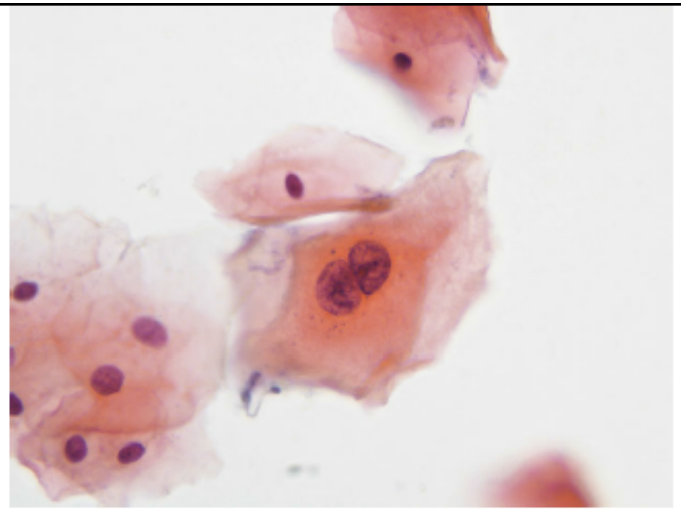


Fig. 4.4 ASC-US (*LBP, ThinPrep*). A 28-year-old female. An atypical binucleated intermediate cell with molded nuclei and orangeophilic cytoplasm suggestive but not diagnostic of LSIL. hrHPV was positive. Follow-up biopsy revealed LSIL (CIN1)

ASC-H

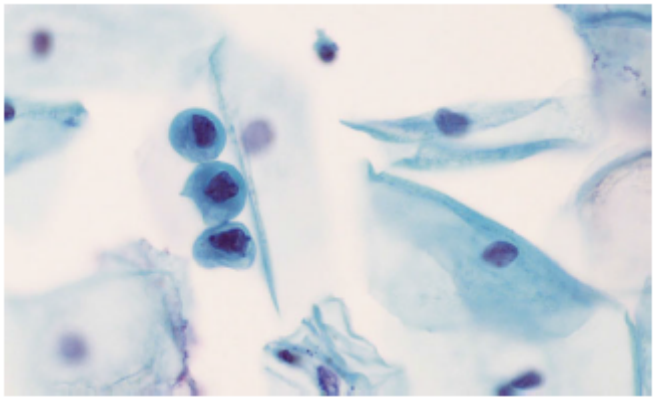


Fig. 4.23 ASC-H (*LBP, SurePath*). Perimenopausal woman with history of atypical cytology (ASC-US). Three small atypical metaplastic cells with hyperchromatic nuclei and irregular nuclear membranes are identified. The interpretive considerations included immature metaplasia; however, a high-grade lesion could not be excluded, thus an interpretation of ASC-H was rendered. Loop electrical excision procedure (LEEP) revealed focal areas of HSIL as well as immature metaplasia. Concomitant review of the cytology favored these cells to represent HSIL

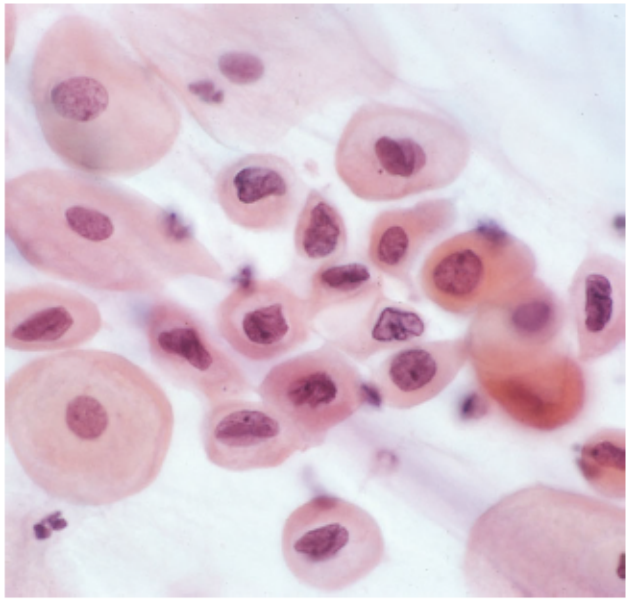


Fig. 4.28 ASC-H (*CP*). Smear from postmenopausal patient containing ovoid cells with irregular poorly preserved nuclei. Possible interpretations include NILM (atrophy), ASC-H and HSIL

ASC-US

- nejčastější závěr (< 3%) - ekonomicky náročné
- ASCUS/LSIL Traige Study (ALTS) - HR HPV test
- doporučení - nad 30 let zvážit HPV test

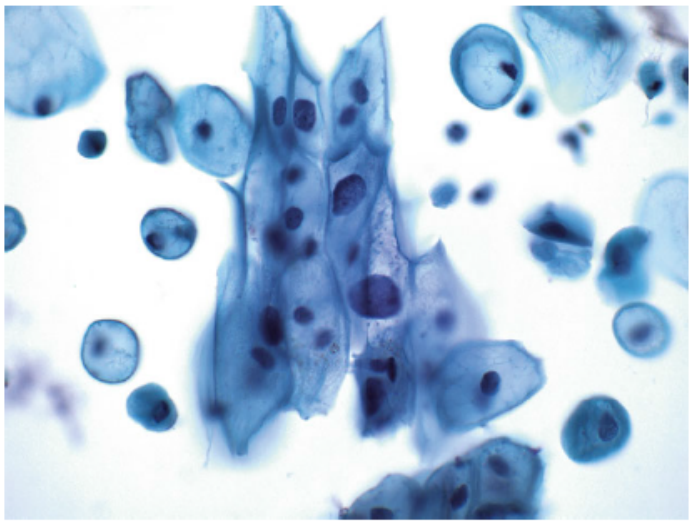


Fig. 4.19 Postmenopausal atypia (*LBP, SurePath*). Postmenopausal woman with an atrophic cell pattern, predominantly comprised of parabasal cells. The presence of occasional enlarged nuclei is a characteristic feature of postmenopausal atypia and is often overcalled as ASC-US. hrHPV testing is usually negative in such cases

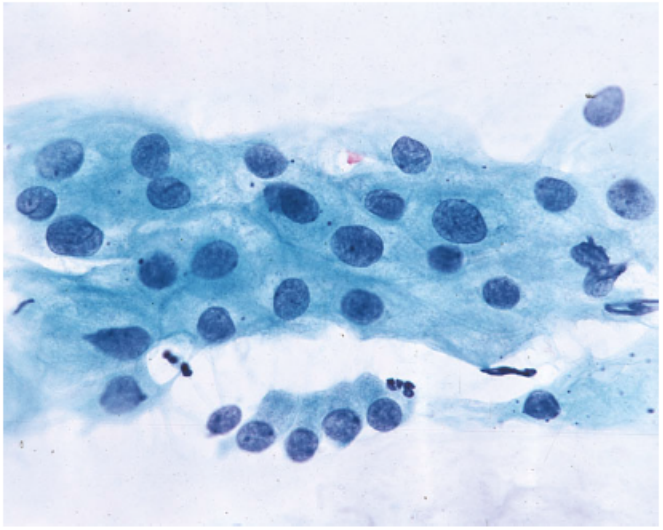


Fig. 4.5 Negative for intraepithelial lesion or malignancy (NILM) versus atypical squamous cells – undetermined significance (ASC-US) (*CP*). Perimenopausal woman. Mature squamous cells show mild nuclear enlargement, binucleation, and even chromatin distribution. Note benign endocervical cells at bottom of field

ASC - H

- **< 10% všech ASC**
- **atypická nezralá metaplázie**
- **nahloučené buněčné trsy**
- **atypická reparace**
- **těžká atrofie**
- **postiradiační změny x susp. recidiva Ca**

ASC-H atypická nezralá metaplázie

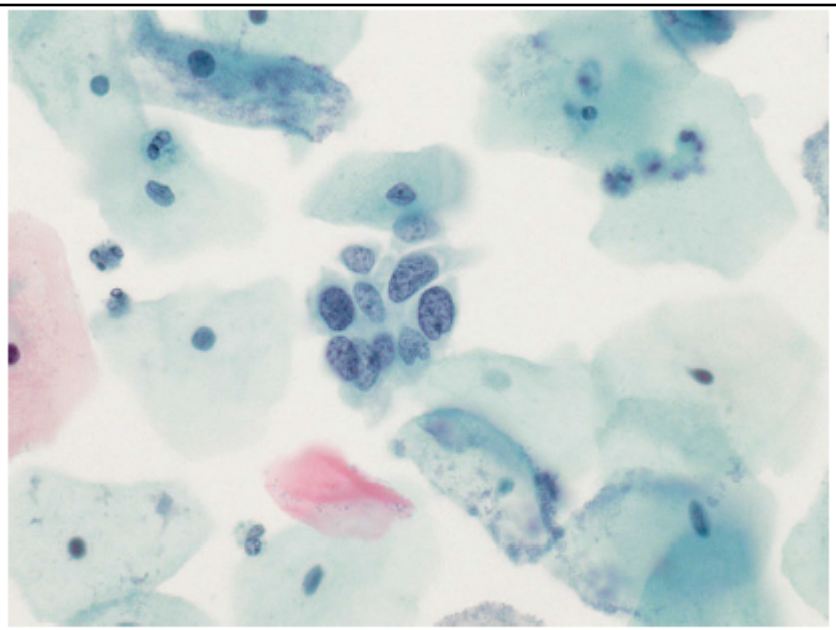


Fig. 4.24 ASC-H (*LBP, SurePath*). A group of atypical immature metaplastic cells with enlarged nuclei, high nuclear to cytoplasmic ratio, coarse chromatin and irregular nuclear contour. The cytologic features are worrisome but insufficient for an interpretation of HSIL. Follow-up biopsy revealed HSIL (CIN3)

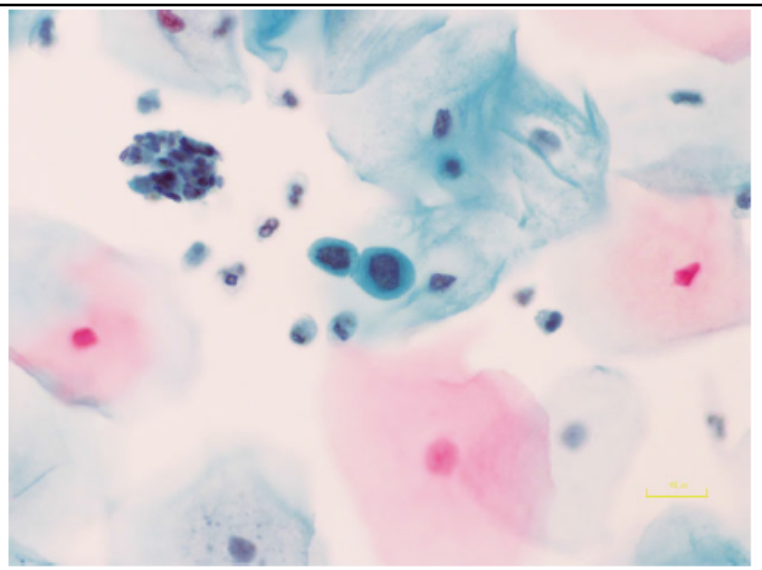


Fig. 4.21 ASC-H (*LBP, SurePath*). Routine cytology for a 30-year-old woman. Rare metaplastic cells with dense cytoplasm and nuclear enlargement with hyperchromasia are present in a background of scattered acute inflammation. An interpretation of ASC-H was rendered. Follow-up cervical biopsies revealed immature squamous metaplasia. Immature squamous metaplasia is one of the most common mimics of HSIL. An interpretation of ASC-H is appropriate, especially when only rare abnormal cells with "metaplastic" cytoplasm and high nuclear to cytoplasmic ratio are present

ASC-H nahloučené bb. trsy

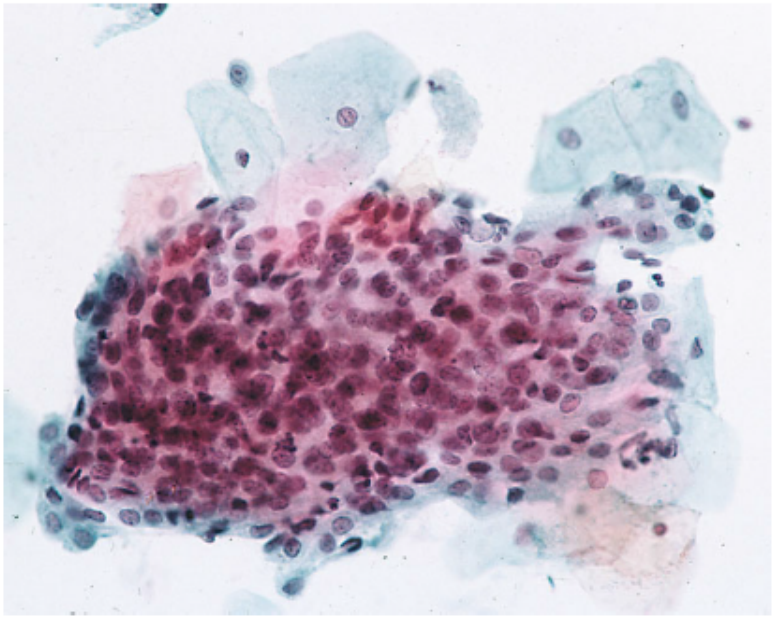


Fig. 4.27 ASC-H (*CP*). Thick aggregate of cohesive, air-dried, overlapping cells containing nuclei with even chromatin and regular borders. The thickness of the cluster makes it difficult to determine if the cells are squamous or glandular. The disorganization of the cells within the group is suggestive of a high-grade lesion; however, the individual nuclear features are insufficient for a definitive interpretation

ASC-H atypická atrofie

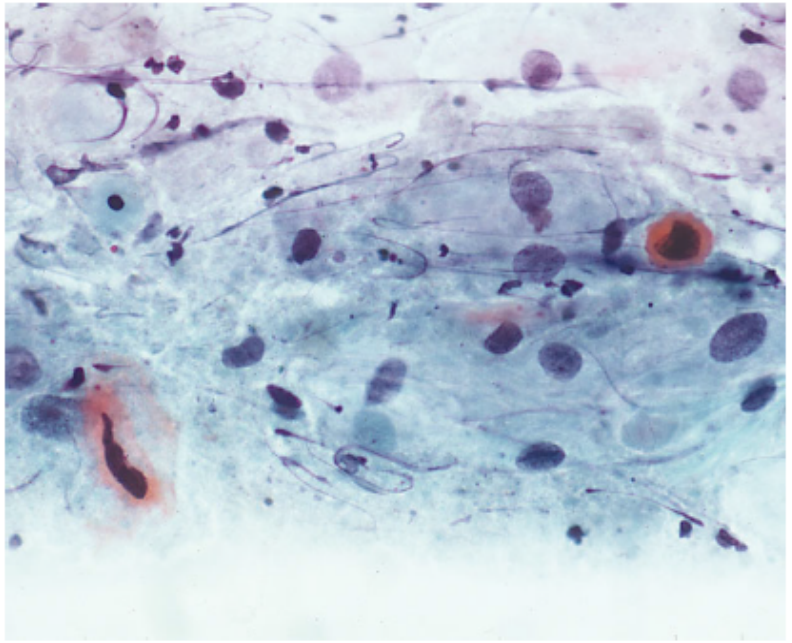


Fig. 4.29 ASC-H (*CP*). A 50-year-old postmenopausal woman with prior abnormal cytology. Two cells with extremely hyperchromatic, degenerated nuclei, and orangeophilic cytoplasm, in a background of atrophy with lysed cells and debris. Follow-up demonstrated HSIL (CIN 2)

ASC-H mimics - degenerované endocervikální a endometrální bb., makrofágy, IUD bb., těhotenské/postpartální stěry

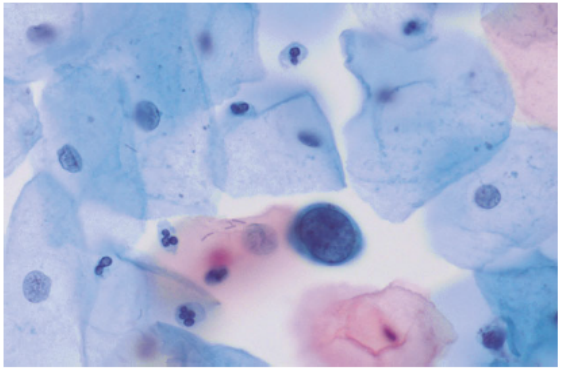


Fig. 4.31 ASC-H (*LBP, SurePath*). Perimenopausal woman with no significant medical history. Cervical cytology was unremarkable with the exception of a single enlarged cell with scant cytoplasm, a distinct, regular nuclear membrane and evenly distributed chromatin. An interpretation of ASC-H was made. Cervical biopsy and endocervical curettage were negative. Cyto-histologic correlation favored this atypical cell to be a degenerated endocervical cell seen *en face*. Review of other fields with comparison of other endocervical cells showed similar nuclear features

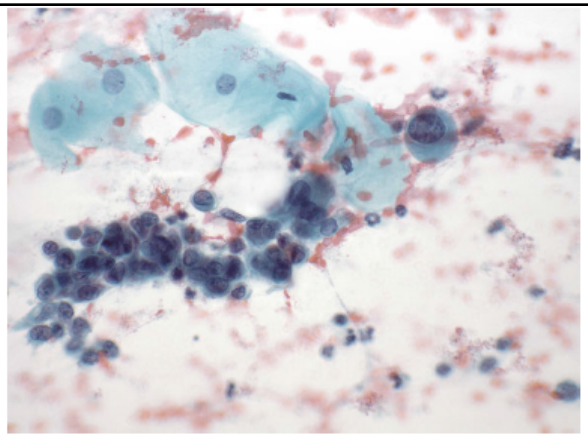


Fig. 4.32 Endometrial cells mimicking HSIL (*CP*). A crowded group of poorly preserved endometrial cells featuring small cells with hyperchromatic nuclei and high nuclear to cytoplasmic ratios

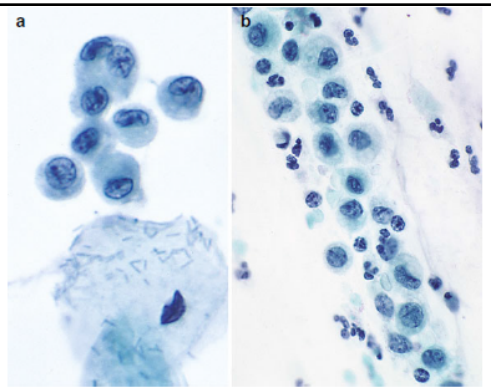


Fig. 4.33 Histiocytes: appearance on liquid based and conventional preparations. (**a**) *Left panel*. NILM, histiocytes (*LBP, ThinPrep*). Routine screen from a 32-year-old woman. Cells possess eccentric oval and round nuclei and foamy cytoplasm. The rounder shape of most cells in *LBP* as compared to *CP* may lead to uncertainty about the cell type; however, definitive assessment is usually possible under high magnification. (**b**) *Right panel*. NILM, histiocytes (*CP*). Streaming pattern of single cells with round, ovoid, and bean-shaped nuclei. Cells possess fine cytoplasmic vacuoles that may resemble degenerative vacuoles sometimes found in normal metaplasia, ASC-H, and HSIL. By contrast, cells of squamous lineage typically are polygonal in shape and possess dense cytoplasm. Follow-up was NILM in both cases

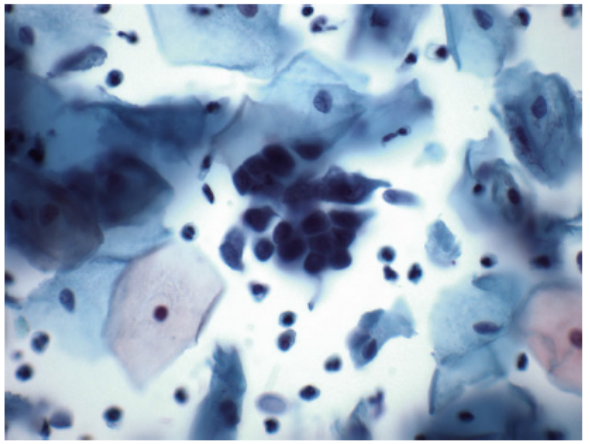


Fig. 4.34 NILM, Endocervical cell grouping (*LBP, SurePath*). Endocervical cells, when viewed on end, may mimic ASC-H, showing high nuclear to cytoplasmic ratios, and a configuration reminiscent of metaplastic cells. Maintenance of a "honey-comb" structure, and a mucus cap when focusing above the nuclear plane is helpful in distinguishing this mimic

SIL - squamous intraepithelial lesion

- tranzientní HPV infekce → prekancerózy → karcinom
  2-stupňový system Bethesda od 1988
- 2012 - Lower Anogenital Squamous Terminology Standartization Consensus Conference (*LAST*) - slizniční i kožní topika
- WHO 2014 - histopatologie - ↓ inter-/ intraobservační variability
- LSIL - koilocytóza, lehká dysplazie, CIN 1
- HSIL - středně těžká a těžká dysplazie, ca in situ, CIN 2-3

LSIL - koilocyty x pseudokoilocyty

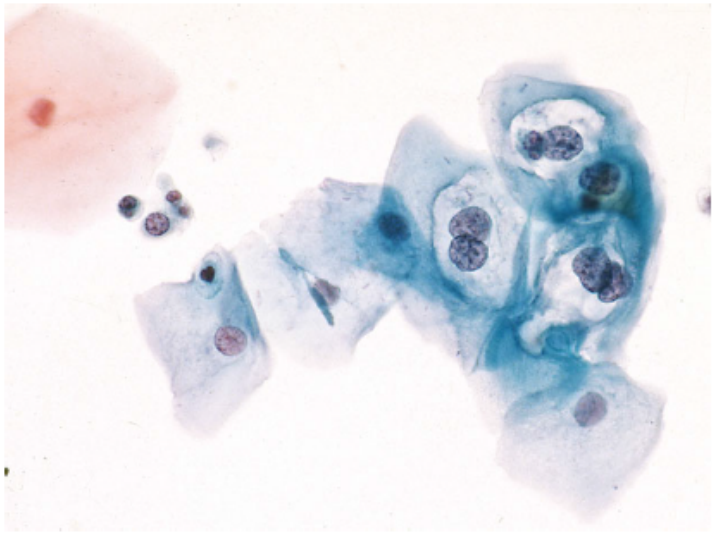


Fig. 5.4 LSIL (*LBP*, *ThinPrep*). Routine screen from a 32-year-old woman. Nuclear abnormalities are required to make an interpretation of LSIL. HPV cytopathic effect manifested by perinuclear cavitation often accompanies the nuclear abnormalities but is not required for an interpretation of LSIL

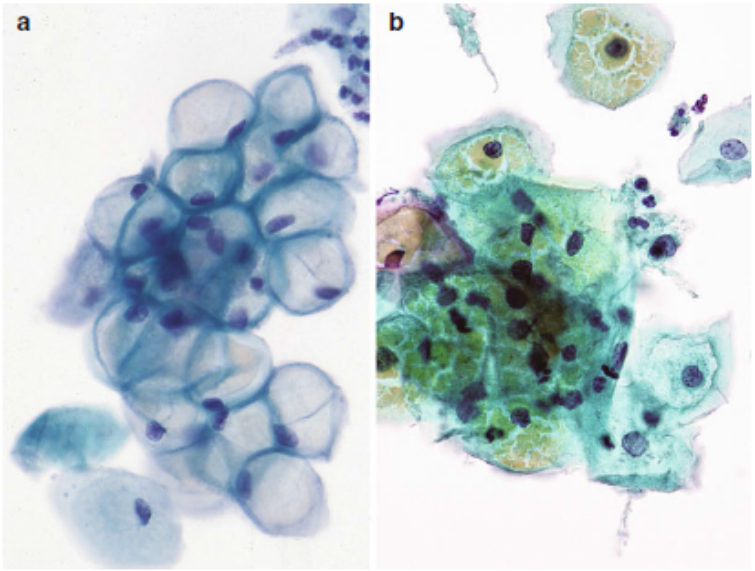


Fig. 5.7 Pseudokoilocytes (*LBP*, *ThinPrep*). Glycogen in squamous cells can give the appearance of "pseudokoilocytosis" (**a**). The halos associated with glycogen often have a yellow refractile appearance (**b**). The nuclear abnormalities required for an interpretation of LSIL are absent. Follow-up in both cases was NILM

HSIL - samostatné bb.

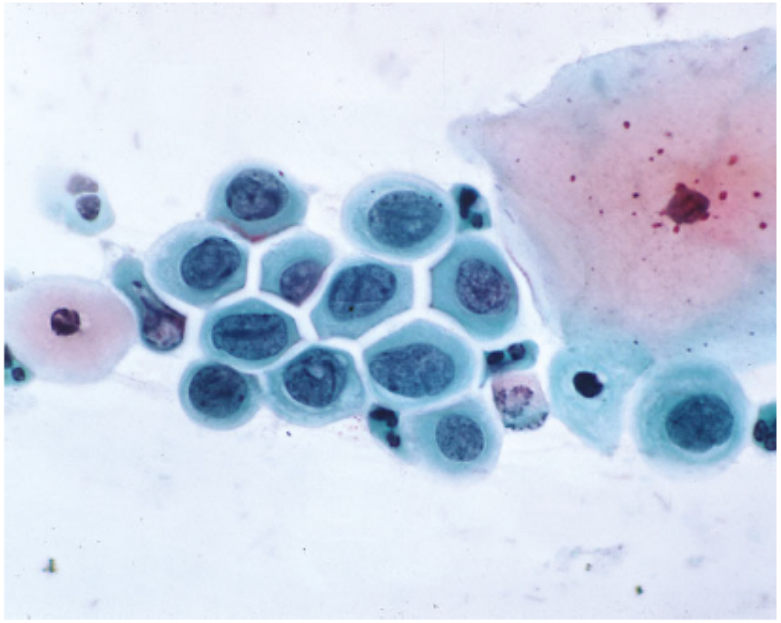


Fig. 5.20 HSIL (*CP*). HSIL with "metaplastic" or dense cytoplasm, in contrast to that seen in the syncytial groups of HSIL (Fig. 5.19)

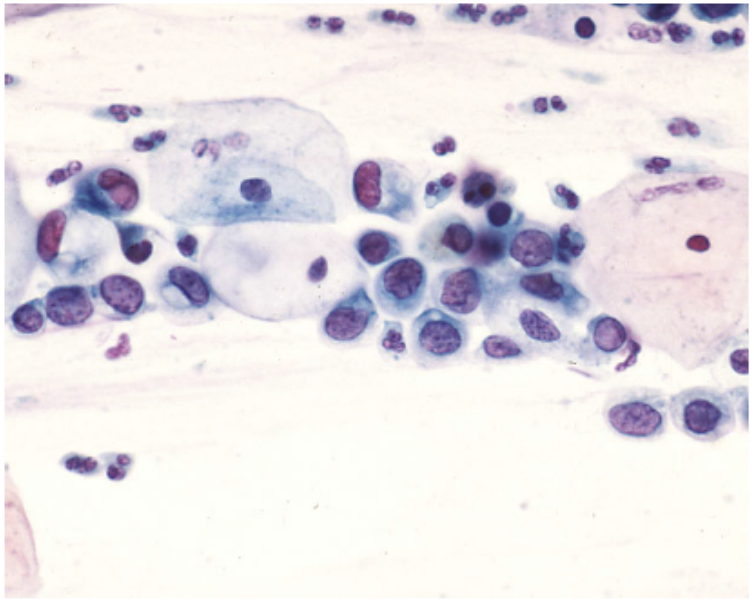


Fig. 5.21 HSIL (*CP*). HSIL cells with some variation in cell size and N/C ratios. A cluster such as this may be misinterpreted as squamous metaplastic cells if examined only under lower magnification. Follow-up showed HSIL (CIN 3)

HSIL - atypická holá jádra

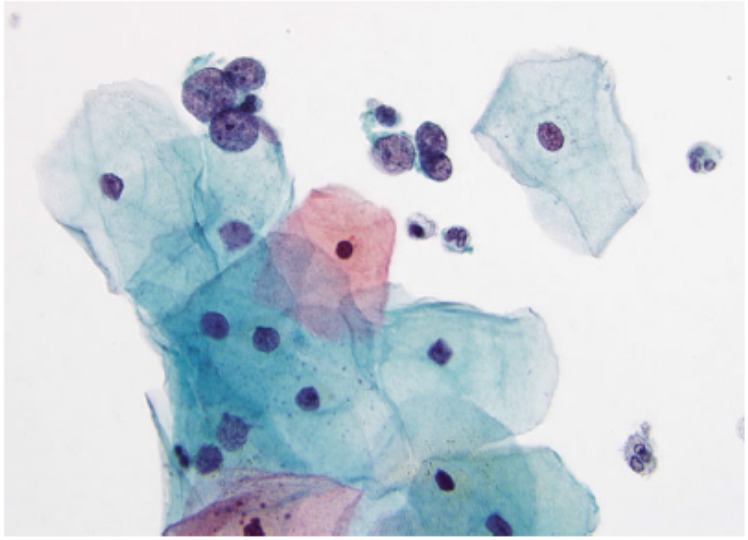


Fig. 5.38 HSIL (*LBP*, *ThinPrep*). Abnormal, large stripped nuclei are seen that are considerably bigger than the intermediate cell nuclei. Such cells should elicit a search for classic, intact HSIL cells elsewhere on the same preparation. These stripped nuclei should be distinguished from endometrial cells or the stripped clusters of atrophic nuclei that are often seen in *LBPs* in the background of atrophy

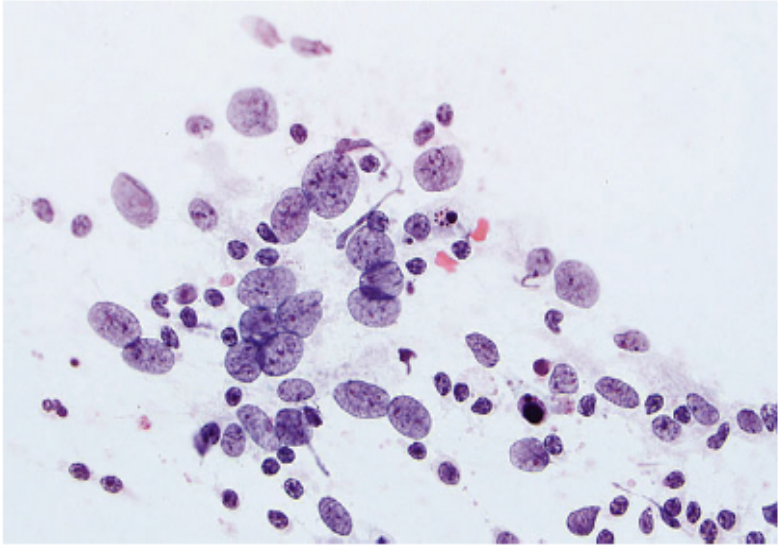


Fig. 5.39 HSIL-stripped nucleus pattern (*CP*). A 38-year-old woman with a history of LSIL. These abnormal stripped nuclei are often a useful diagnostic clue that other abnormal cells may be identified on the same slide. They should be distinguished from the bare intermediate cell nuclei seen in cytolysis (Fig. 2.62) and from "small blue cells" (see Fig. 3.7)

HSIL - glandulární extenze

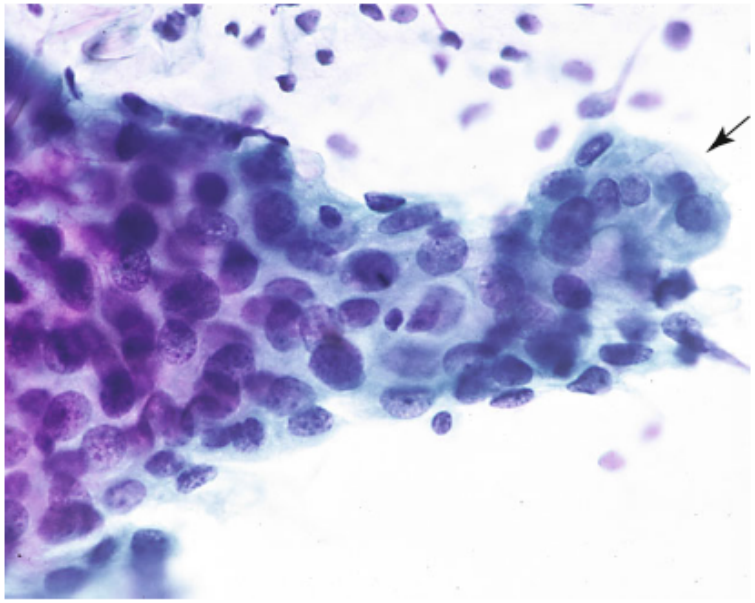


Fig. 5.33 HSIL (*CP*). A 30-year-old woman with atypical glandular cells on a prior Pap test. When HSIL lesions involve endocervical glands, they may show features that overlap with those of adenocarcinoma in situ (AIS). Note normal columnar cells with residual mucin at the *right upper edge* of the cell cluster (*arrow*). Follow-up showed CIN with endocervical gland involvement

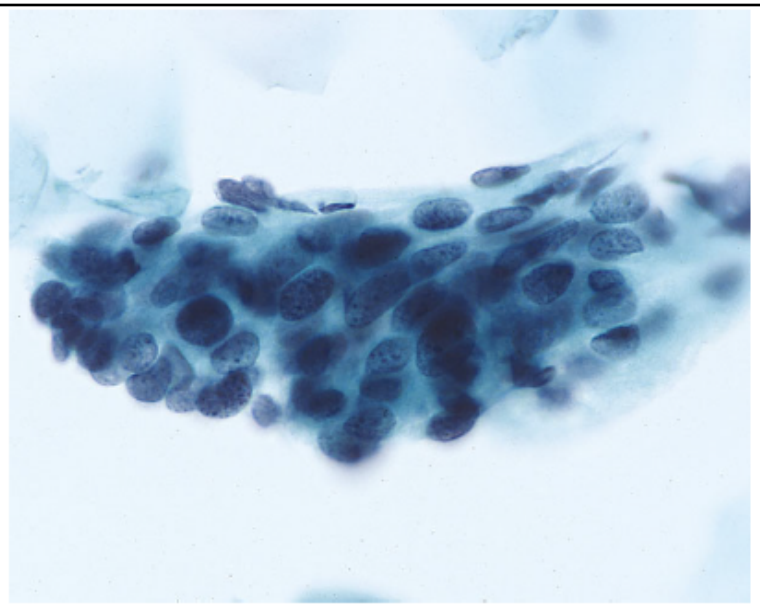


Fig. 5.34 HSIL (*LBP*, *SurePath*). A 44-year-old woman. Syncytial cluster of HSIL cells with features of endocervical gland extension. Such "hyperchromatic crowded groups" may raise a wide differential diagnosis under low magnification; attention to architectural pattern and cellular detail are necessary for correct interpretation. Follow-up showed HSIL (CIN 3) with endocervical gland involvement

LSIL nebo HSIL ?

- v terénu LSIL bb. suspektní z HSIL
- návrh : „LSIL, cannot exclude HSIL“ / „LSIL-H“
- zamítnuto : 3-stupňový systém
- v histologii ↑ HSIL (CIN2+) než LSIL
- LSIL + oj. bb. HSIL → HSIL
- LSIL + bb. susp. HSIL → LSIL + ASC-H
- management - kolposkopie/biopsie, u mladých žen kolposkopie
- malé množství nálezů

LSIL, ASC-H event. LSIL s komentářem možné HSIL

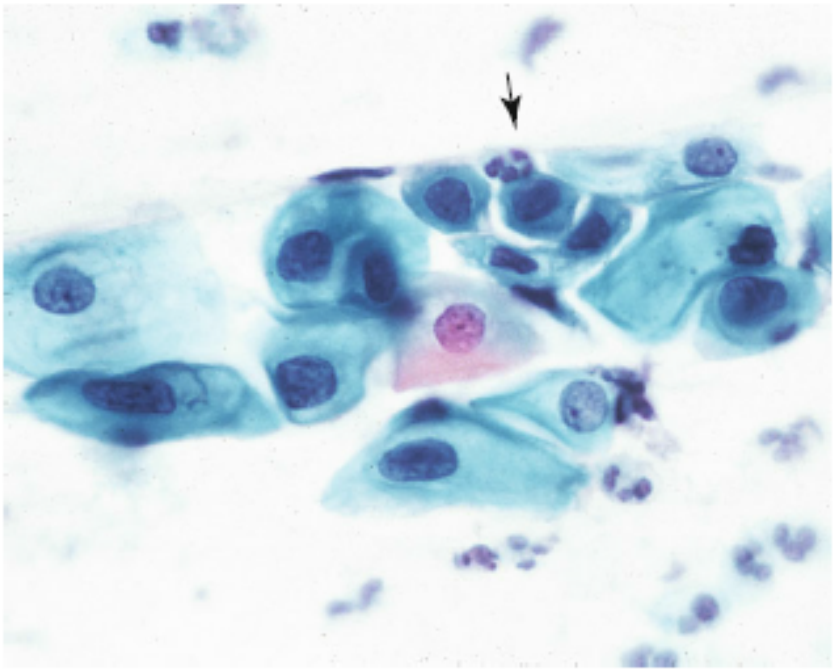


Fig. 5.47 LSIL with some cells suggesting the possibility of a concurrent HSIL (*CP*). Routine screen from a 28-year-old woman. Most of these cells qualify as LSIL; however, there are three atypical metaplastic cells at the top center (*arrow*) that raise the possibility of a high-grade lesion. Cases such as this are may be interpreted as LSIL with a comment explaining the possibility of HSIL or as LSIL with an additional interpretation of ASC-H. The presence of a few diagnostic HSIL cells in the background of a predominant LSIL pattern should be interpreted as HSIL. Follow-up in this case showed HSIL (CIN 2)

6.1 Epithelial Cell Abnormalities

Glandular Cell

- Atypical
  - Endocervical cells (NOS or specify in comments)
  - Endometrial cells (NOS or specify in comments)
  - Glandular cells (NOS or specify in comments)
- Atypical
  - Endocervical cells, favor neoplastic
  - Glandular cells, favor neoplastic

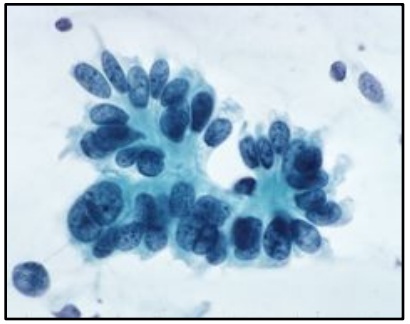
- Endocervical adenocarcinoma in situ (AIS)
- Adenocarcinoma
  - Endocervical
  - Endometrial
  - Extrauterine
  - Not otherwise specified (NOS)

Glandulární abnormality

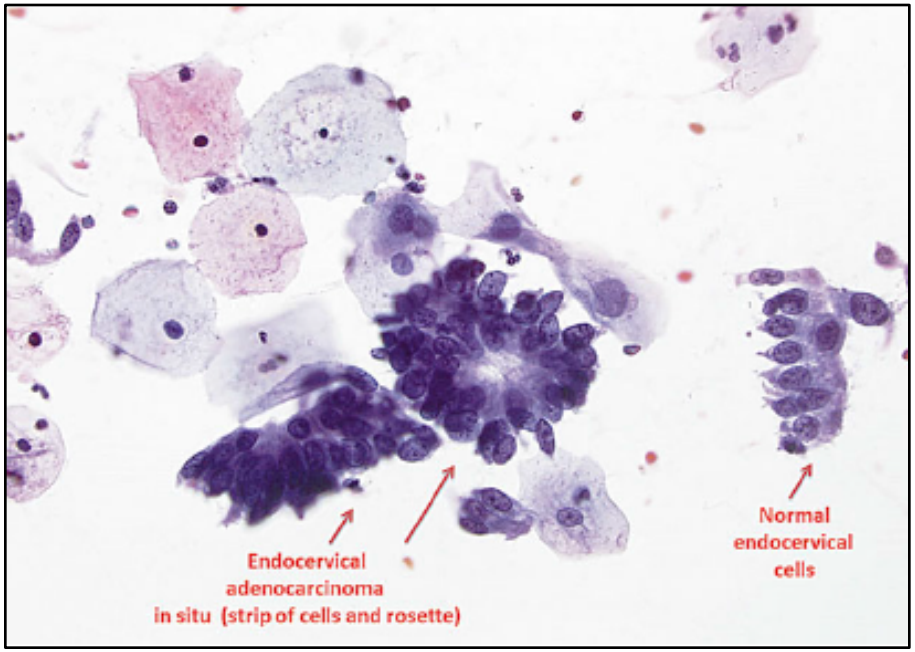
AIS, adenokarcinom, nonneoplastické procesy - DDS, tubální metaplázie, reparace, zánět, polypy, mikroglandulární hyperplazie, postradiační změny, Arias-Stela reakce

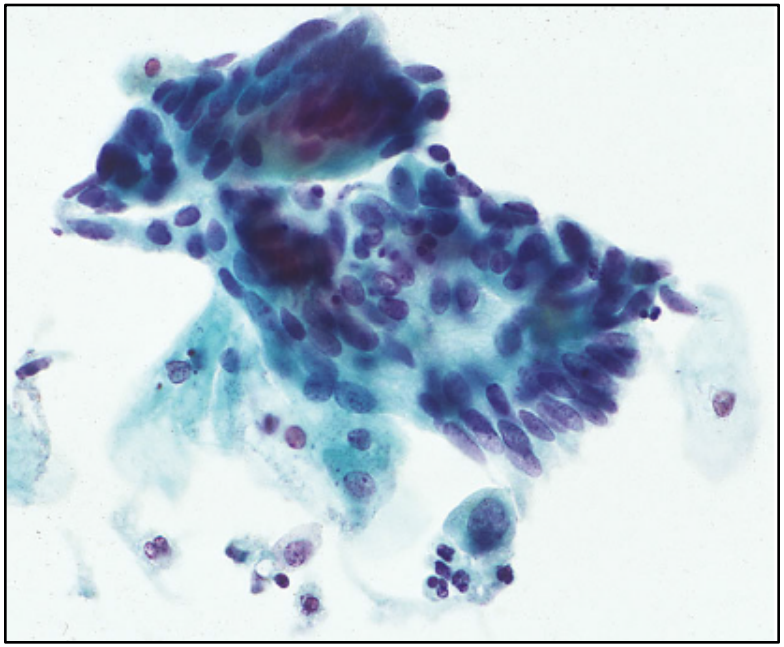
1. **skríning primárně pro dlaždicové abnormality**
2. **↑ incidence cervikálních adenokarcinomů**
3. **odběrové nástroje**
4. **obtížné hodnocení**

Cervikální adenokarcinom, AIS



- závěry AGC v definitivní histologii většinou dlaždicové léze
- mimikr - HSIL s postižením endocervikálních krypt
- HPV negat. > 35 let , symptomy - endometriální sampling





Sekundární nádory či metastázy

- **přímé prorůstání** - endometrium, močový měchýř, rektum
- **lymfogenně a hematogenně** - GIT, ovária, prs
- **exfoliované bb. přes tuby** - ovária, tuby, peritoneum

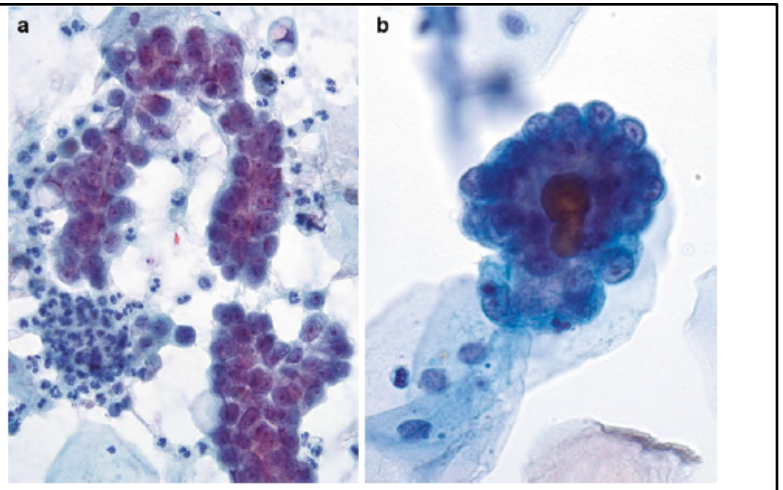


Fig. 7.17 Ovarian carcinoma. Papillary clusters with scalloped border consisting of large overlapping cells with round nuclei, prominent nucleoli, and moderate amounts of cytoplasm showing eccentrically placed vacuoles (**a** *left*, *CP*). Similar papillary clusters comprise cells with enlarged nuclei with finely granular chromatin and prominent nucleoli. Occasional psammoma bodies are seen in ovarian carcinoma (**b** *right*, *LBP*, *ThinPrep*)

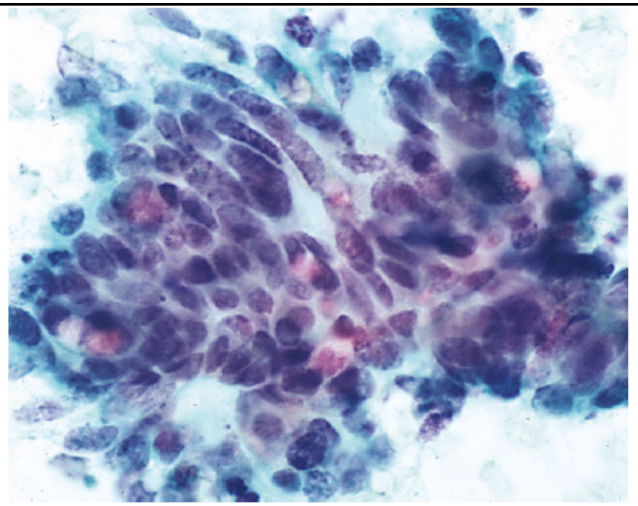


Fig. 7.14 Metastatic colon carcinoma (*CP*). A group of tall columnar glandular cells demonstrates nuclear pleomorphism, hyperchromasia, cellular overlap, and loss of polarity within the cell group. These morphologic features would lead to an interpretation of malignancy. The columnar cell shape, palisading cigar-shaped nuclei, and scattered goblet cells containing distended mucin-filled vacuoles seen in this image are distinctive morphologic features of colonic adenocarcinoma, as is "dirty necrosis" (not shown here)

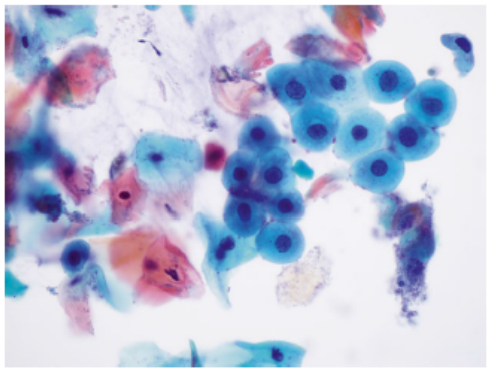


Fig. 8.2 Negative for intraepithelial lesion (*LBP, ThinPrep*). Several round squamous metaplastic cells with dense cytoplasm are present

Anální cytologie

- **incidence ca anu - ♀1,5/♂0,8/ 100 000**
- **až 90% HPV infekce**
- **↑riziko - MSM, HIV+, po transplantacích, ♀s anamnézou multicentrické genitální neoplazie**
- **sensitivita pro HSIL 70 - 90 %**
- **nižší korelace gradu cytologie x biopsie**
- **suspektní nálezy → HRA + biopsie**

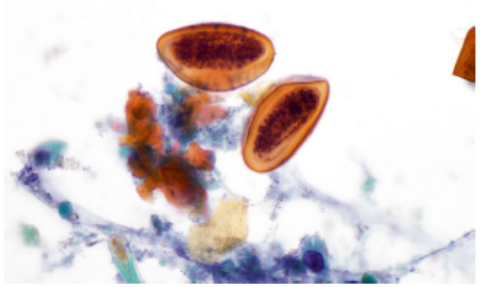


Fig. 8.10 Pinworm eggs (*LBP, ThinPrep*)

Skríningové modely

	Cytology	HPV	Cotesting (Cytology and HPV)
Sensitivity	Lowest	Higher	Highest
Repeat interval for negative screen	Shortest (highest cNPV)	Longer (lower cNPV)	Longest (lowest cNPV)
Number of women with positive screening results	Lowest	Higher	Highest
Triage test required	For equivocal cytology results	For all positive results	For all HPV-positive, cytology-negative results
Triage test options	HPV Repeat cytology Biomarkers	Cytology HPV genotyping Biomarkers	Repeat cotest HPV genotyping Biomarkers
Diagnostic test	Colposcopic biopsy		

Nová kapitola
„ *Risk Assessment Aproach to Management* “

- *„similar management for similar risk“*
- **začlenění HPV testu do skríningového algoritmu**
- ***ASCUS/LSIL Triage study (ALTS)*** **- HPV+ ASCUS = LSIL**
- **stanovení rizika - HPV test, genotyping 16/18, cytologie, biomarkery (imunohistochemické *p16/ki67*, molekulárně genetické *metylace*)**

cervikální cytologie : samostatný test
cotest
triage pozitivních ♀ v primárním HPV skríningu

„similar risk to similar management“

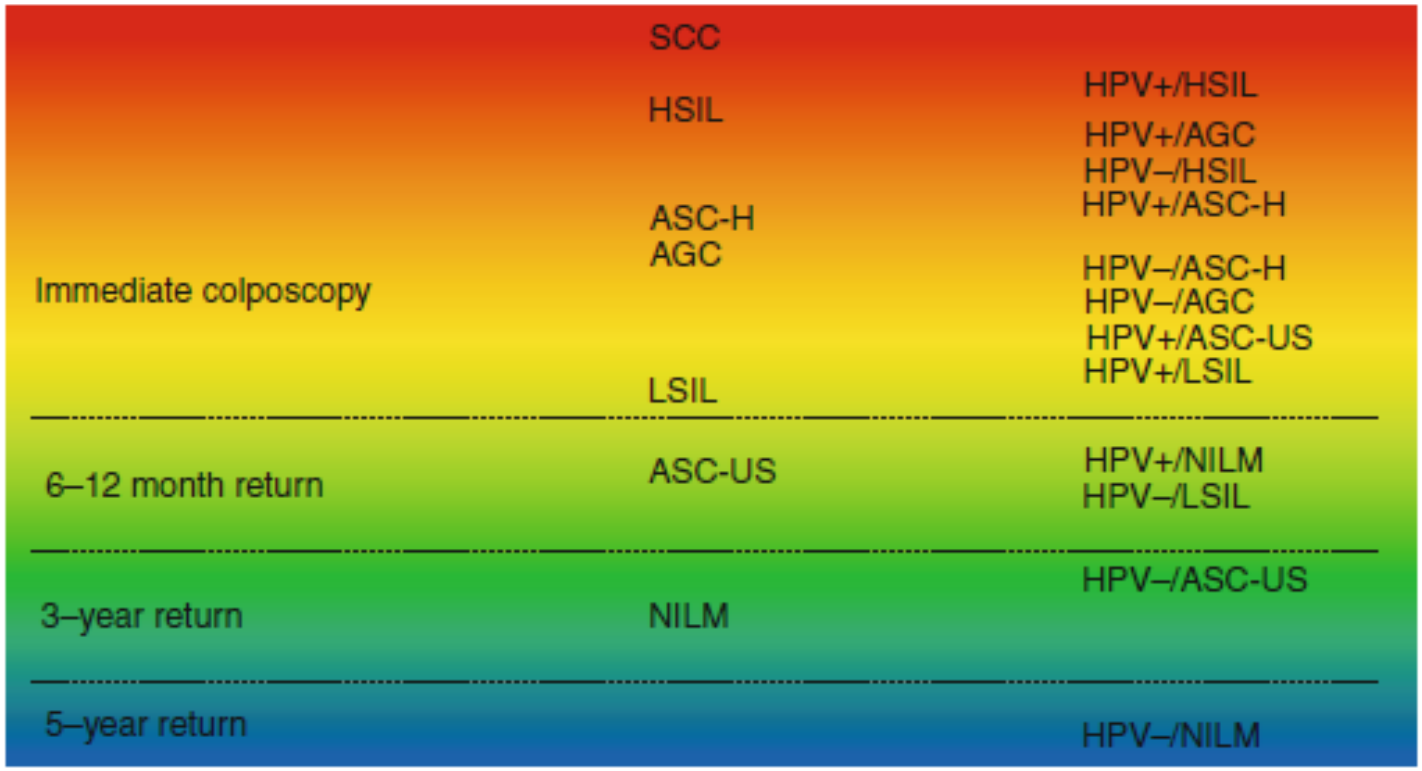


Fig. 12.2 Risk benchmarks for 2012 ASCCP management guidelines. Absolute risk of cervical precancer is shown on the *y*-axis. Cytology results and co-testing results are grouped in their respective risk categories with different management strategies [2, 7]

Děkuji za pozornost