

The Bethesda system Negative/Benign change in the Female Genital Tract

Jun Kang

2022 6 18

BETHESDA SYSTEM FOR REPORTING CERVICAL CYTOLOGY

"The terms "interpretation" or "result" are recommended instead of "diagnosis" in the heading of the cervical cytology report. This terminology is preferred because cervical cytology should be viewed primarily as a screening test."

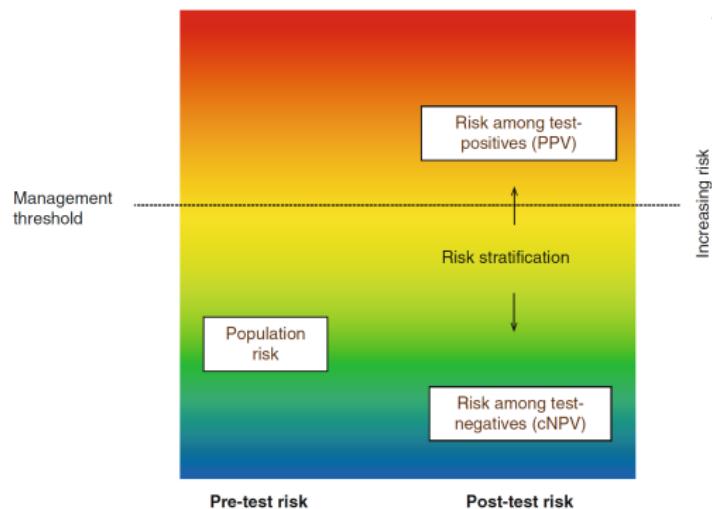
Screening test

“ Screening test, which in some instances may serve as a medical consultation by providing an interpretation that contributes to a diagnosis .”

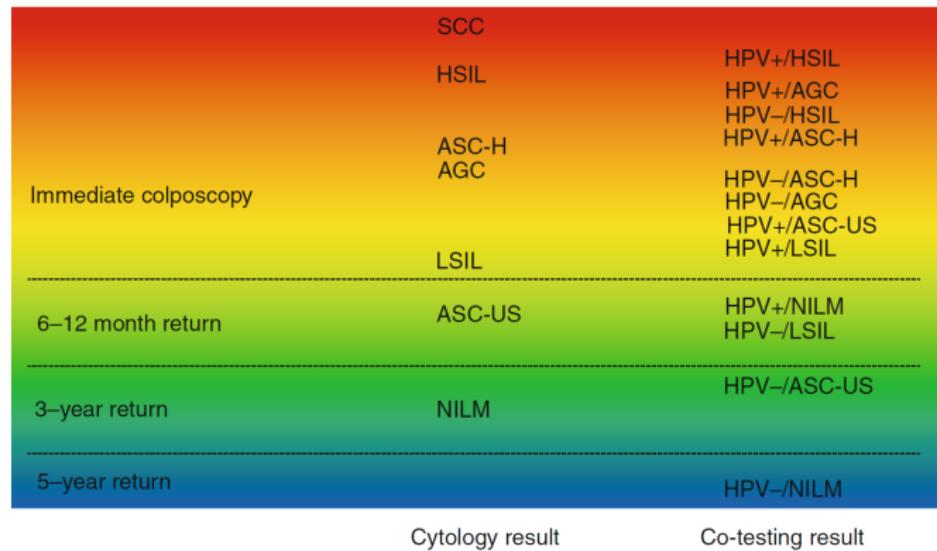
BETHESDA SYSTEM FOR REPORTING CERVICAL CYTOLOGY

" A patient's final diagnosis and management plan integrate not only the cervical cytology result but also the history, clinical findings, and other laboratory results such as molecular/biomarker testing and biopsy interpretations "

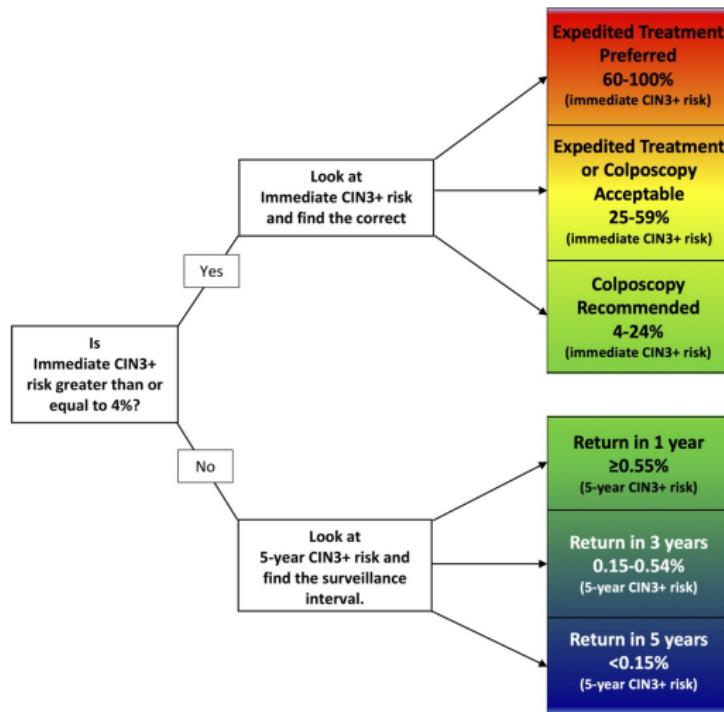
Risk Assessment Approach to Management



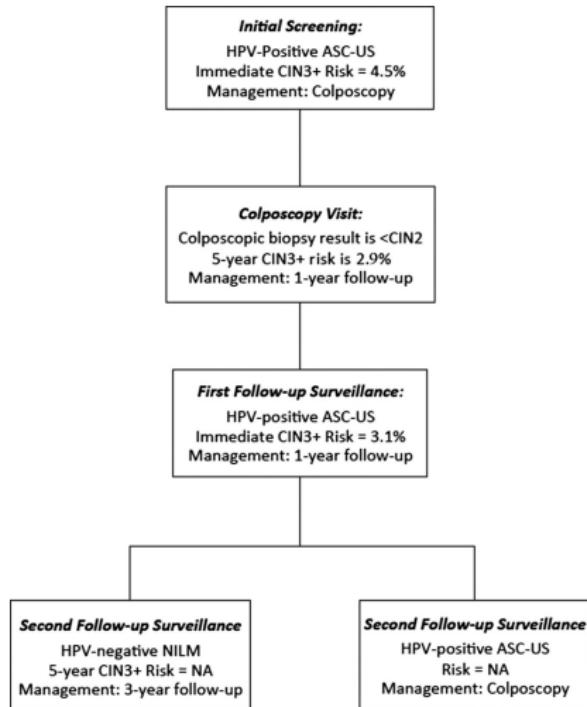
Risk Assessment Approach to Management



2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors



Management example



The 2014 BETHESDA SYSTEM FOR REPORTING CERVICAL CYTOLOGY

- ▶ Additional experience with morphology on liquid-based preparations
- ▶ Further insights into HPV biology
- ▶ Implementation of HPV vaccination
- ▶ Updated guidelines for cervical cancer screening and the management of abnormal cervical cytology and cancer precursors

Specimen Adequacy

SPECIMEN TYPE:

- ▶ Indicate conventional smear (Pap smear) vs. liquid-based preparation vs. other

SPECIMEN ADEQUACY

- ▶ Satisfactory for evaluation (describe presence or absence of endocervical/transformation zone component and any other quality indicators, e.g., partially obscuring blood, Inflammation, etc.)
- ▶ Unsatisfactory for evaluation . . . (specify reason)
 - ▶ Specimen rejected/not processed (specify reason)
 - ▶ Specimen processed and examined, but unsatisfactory for evaluation of epithelial abnormality because of (specify reason)

GENERAL CATEGORIZATION (optional)

- ▶ Negative for Intraepithelial Lesion or Malignancy
- ▶ Other: See Interpretation/Result (e.g., endometrial cells in a woman ≥ 45 years of age)
- ▶ Epithelial Cell Abnormality: See Interpretation/Result (specify 'squamous' or 'glandular' as appropriate)

INTERPRETATION/RESULT

NEGATIVE FOR INTRAEPITHELIAL LESION OR MALIGNANCY
(When there is no cellular evidence of neoplasia, state this in the General Categorization above and/or in the Interpretation/Result section of the report – whether or not there are organisms or other non-neoplastic findings)

NON-NEOPLASTIC FINDINGS (optional to report)

- ▶ Non-neoplastic cellular variations
- ▶ Squamous metaplasia
- ▶ Keratotic changes
- ▶ Tubal metaplasia
- ▶ Atrophy
- ▶ Pregnancy-associated changes

NON-NEOPLASTIC FINDINGS

- ▶ 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

OTHER

- ▶ Endometrial cells (in a woman ≥ 45 years of age)
(Specify if “negative for squamous intraepithelial lesion”)

EPITHELIAL CELL ABNORMALITIES SQUAMOUS CELL

- ▶ Atypical squamous cells
 - ▶ of undetermined significance (ASC-US)
 - ▶ cannot exclude HSIL (ASC-H)
- ▶ Low-grade squamous intraepithelial lesion (LSIL) (encompassing: HPV/mild dysplasia/CIN 1)
- ▶ High-grade squamous intraepithelial lesion (HSIL) (encompassing: moderate and severe dysplasia, CIS; CIN 2 and CIN 3)
 - ▶ with features suspicious for invasion (if invasion is suspected)
- ▶ Squamous cell carcinoma

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

EPITHELIAL CELL ABNORMALITIES

- ▶ Endocervical adenocarcinoma in situ
- ▶ Adenocarcinoma
 - ▶ endocervical
 - ▶ endometrial
 - ▶ extrauterine
 - ▶ not otherwise specified (NOS)

OTHER MALIGNANT NEOPLASMS: (specify)

ADJUNCTIVE TESTING

Provide a brief description of the test method(s) and report the result so that it is easily understood by the clinician.

COMPUTER-ASSISTED INTERPRETATION OF CERVICAL CYTOLOGY

If case examined by an automated device, specify device and result.

EDUCATIONAL NOTES AND COMMENTS APPENDED TO CYTOLOGY REPORTS (optional)

Suggestions should be concise and consistent with clinical follow-up guidelines published by professional organizations (references to relevant publications may be included).

Adequacy Categories

- ▶ Satisfactory
- ▶ Satisfactory for evaluation
 - ▶ (describe presence or absence of endocervical/ transformation zone component and any other quality indicators, e.g., partially obscuring blood, Inflammation, etc., as appropriate)

Adequacy Categories

- ▶ Unsatisfactory
 - ▶ For unsatisfactory specimens, indicate whether or not the laboratory has processed/evaluated the slide. Suggested wording:
 - ▶ A. Rejected specimen: specimen rejected (not processed) because _____ (specimen not labeled, slide broken, etc.)
 - ▶ B. Fully evaluated, unsatisfactory specimen: Specimen processed and examined but unsatisfactory for evaluation of epithelial abnormality because of _____ (obscuring blood, etc.)
 - ▶ Additional comments/recommendations, as appropriate

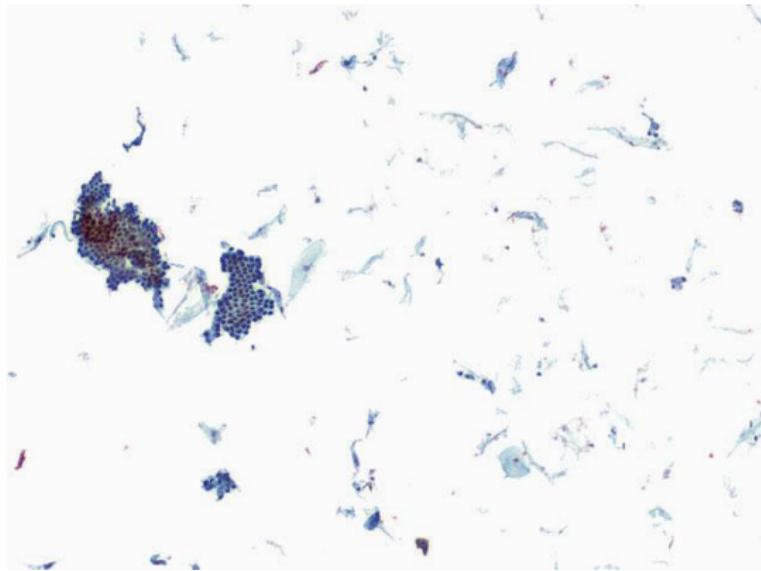
Guidelines for estimating cellularity of liquid-based preparations

Table 1.1 Guidelines for estimating cellularity of liquid-based preparations

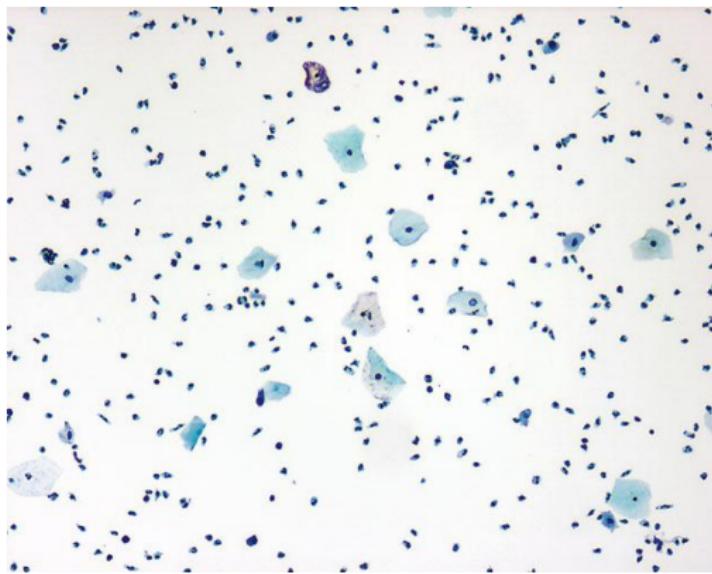
		FN20 eyepiece/10× objective		FN20 eyepiece/40× objective		FN22 eyepiece/10× objective		FN22 eyepiece/40× objective	
Prep. diameter (mm)	Area (mm ²)	Number of fields at FN20, 10×	Number of cells/field for 5K total	Number of fields at FN20, 40×	Number of cells/field for 5K total	Number of fields at FN22, 10×	Number of cells/field for 5K total	Number of fields at FN22, 40×	Number of cells/field for 5K total
13	132.7	42.3	118.3	676	7.4	34.9	143.2	559	9.0
20	314.2	100	50.0	1,600	3.1	82.6	60.5	1,322	3.8

FN field number

Unsatisfactory due to scant squamous cellularity

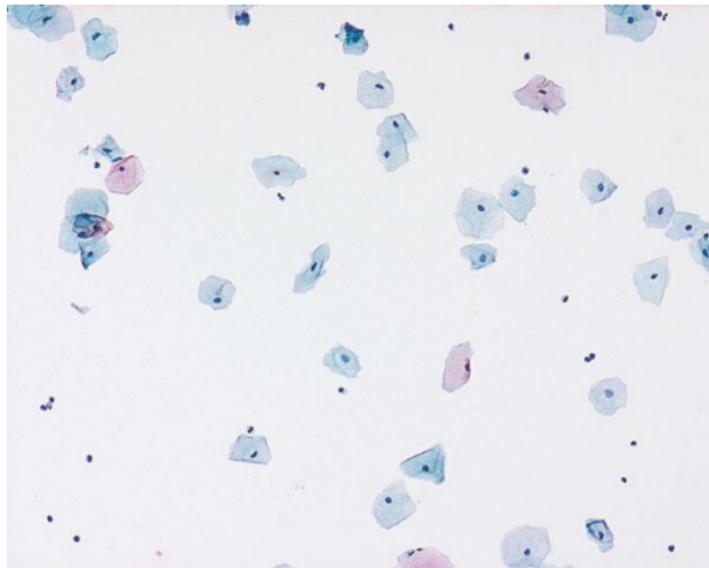


Unsatisfactory + scant cellularity (LBP, SurePath)



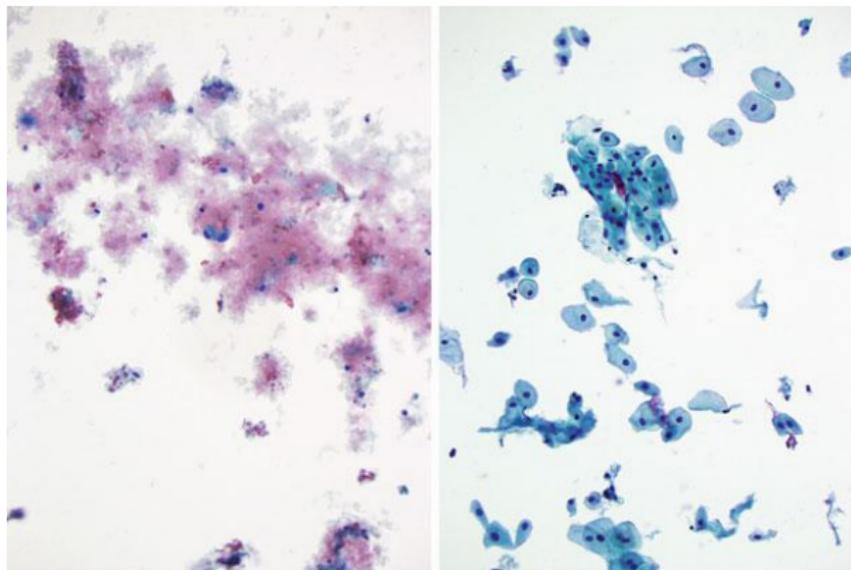
SurePath slide had fewer than 8 cells per $40\times$ field. A SurePath specimen with this level of cellularity throughout the preparation would have fewer than 5,000 cells

Satisfactory, but borderline squamous cellularity (LBP, SurePath)



At 40 \times , there were approximately 11 cells per field when ten microscopic fields along a diameter were evaluated for squamous cellularity; this would give an estimated total cell count between 5,000 and 10,000

Unsatisfactory specimen

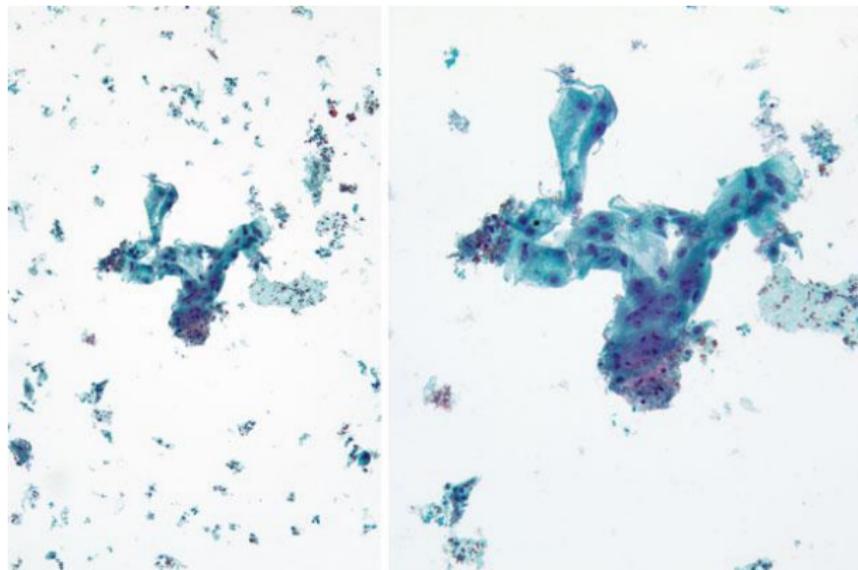


Original preparation (a , left) unsatisfactory due to scant squamous cellularity and excessive blood (LBP, ThinPrep). Reprocessing with glacial acetic acid resulted in a satisfactory sample (b , right)

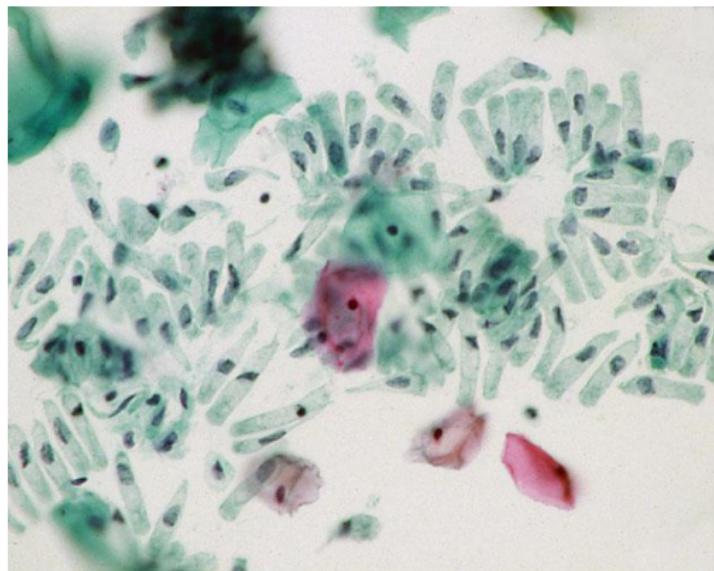
Satisfactory vaginal cytology from a 56-year-old, status post total hysterectomy



Low-cellularity but satisfactory specimen in woman with history of radiation

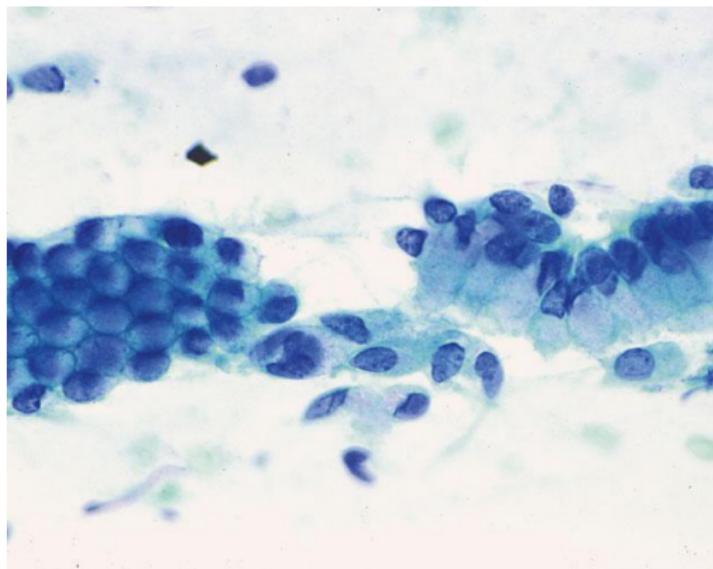


Endocervical/Transformation Zone (EC/TZ) Component



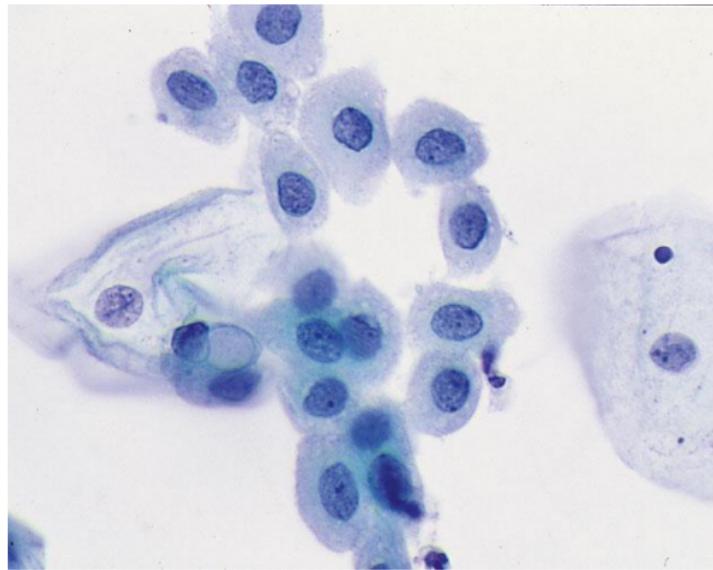
Cellular dissociation is more frequent in liquid- based preparations

Endocervical/Transformation Zone (EC/TZ) Component

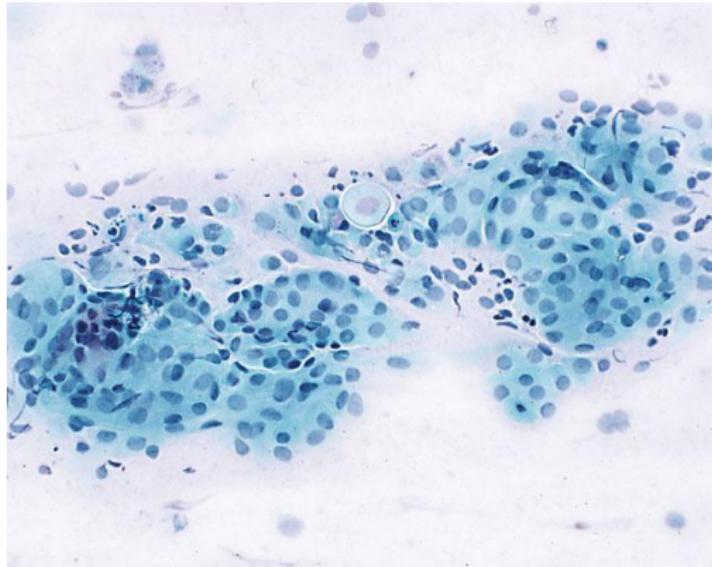


"honeycomb" "picket fence"

Normal squamous metaplastic cells



Atrophy (CP)

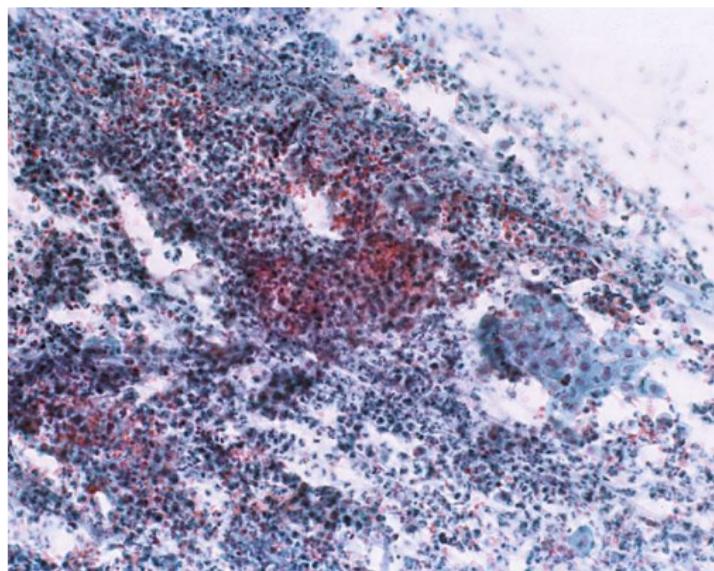


Degenerated cells in mucus and parabasal-type cells should not be counted in assessing transformation zone sampling.

Obscuring Factors

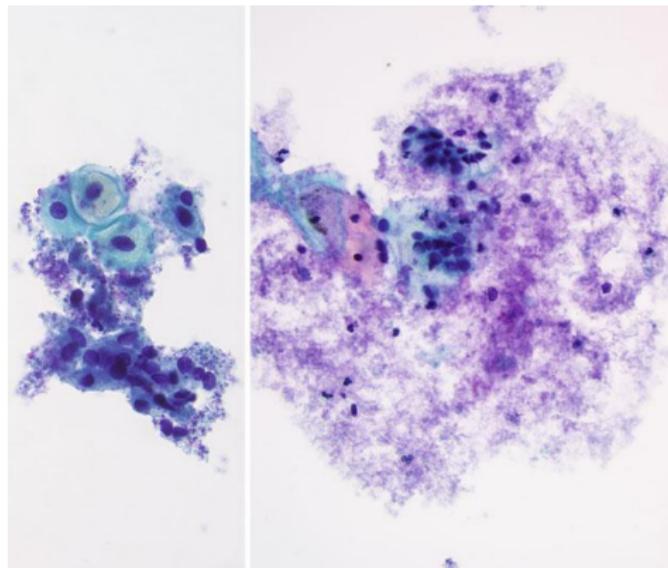
- ▶ 75 % of squamous cells are obscured: unsatisfactory
 - ▶ No abnormal cells are identified
- ▶ 50–75% obscured: partially obscured
- ▶ Nuclear preservation and visualization: key importance

Unsatisfactory due to obscuring white blood cells (CP).



50–75 % of the epithelial cells are covered, obscuring inflammation

Unsatisfactory due to excess lubricant; 59-year-old woman (LBP , ThinPrep).



Lubricant may mimic blood or mucus at low magnification

Non-Neoplastic Findings

- ▶ Negative for Intraepithelial Lesion or Malignancy
 - ▶ No cellular evidence of neoplasia
 - ▶ Organisms or other nonneoplastic findings (optional to report)

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

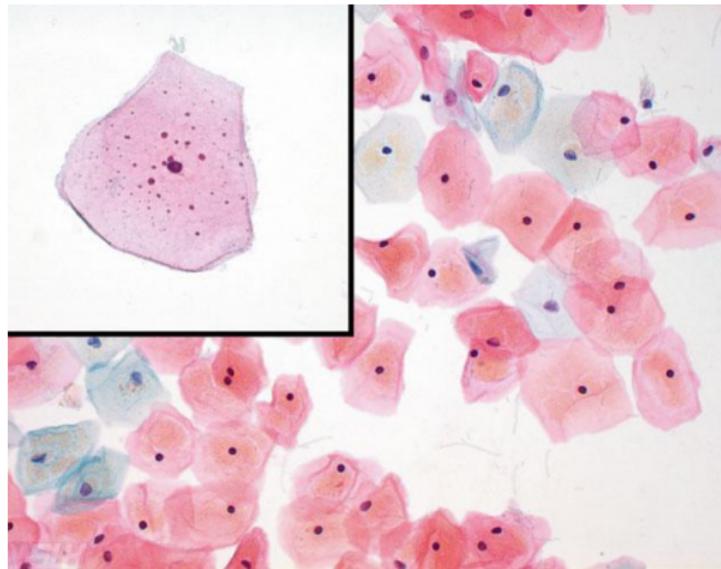
Nonneoplastic Findings (Optional to Report)

- ▶ Reactive cellular changes associated with:
 - Inflammation (includes typical repair)
 - Lymphocytic (follicular) cervicitis
 - Radiation
 - Intrauterine contraceptive device (IUD)
- ▶ Glandular cells status post hysterectomy

Nonneoplastic Findings (Optional to Report)

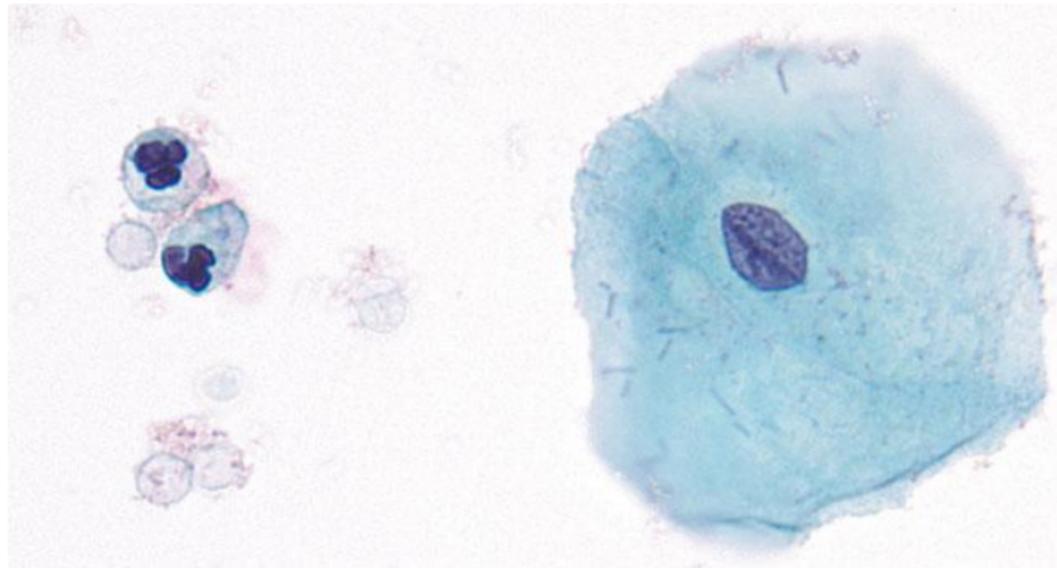
- ▶ Organisms
- ▶ *Trichomonas vaginalis*
- ▶ Fungal organisms morphologically consistent with *Candida* spp.
- ▶ Shift in flora suggestive of bacterial vaginosis
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- ▶ Cellular changes consistent with herpes simplex virus
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Superficial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



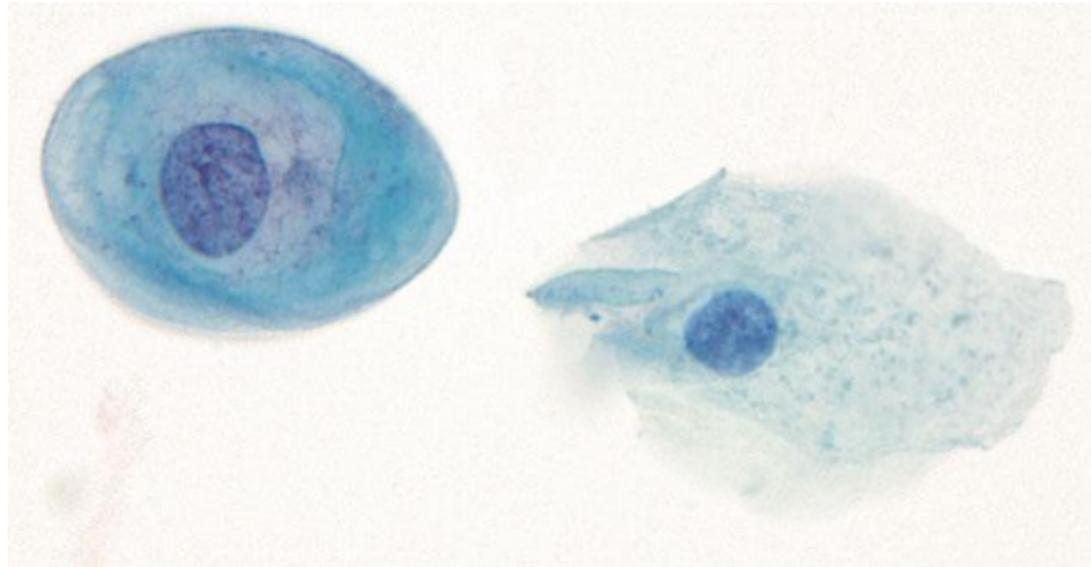
Admixture of superficial and intermediate squamous cells. The superficial cells have smaller condensed (pyknotic) nuclei. Light brown glycogen is present in the cytoplasm of both cell types.

Intermediate Cell



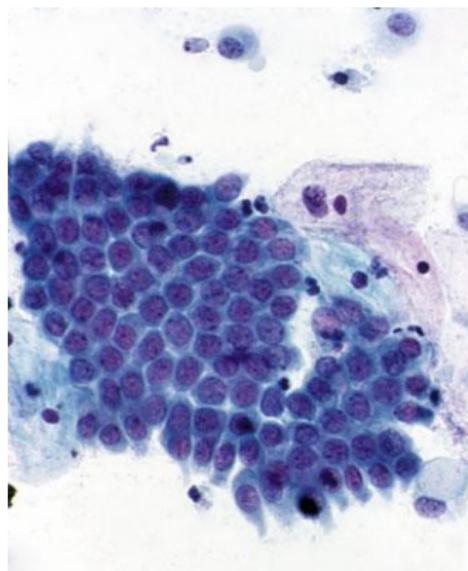
A typical intermediate cell with a polygonal cytoplasmic profile. The nucleus possesses finely granular chromatin with a longitudinal groove.

Parabasal cell



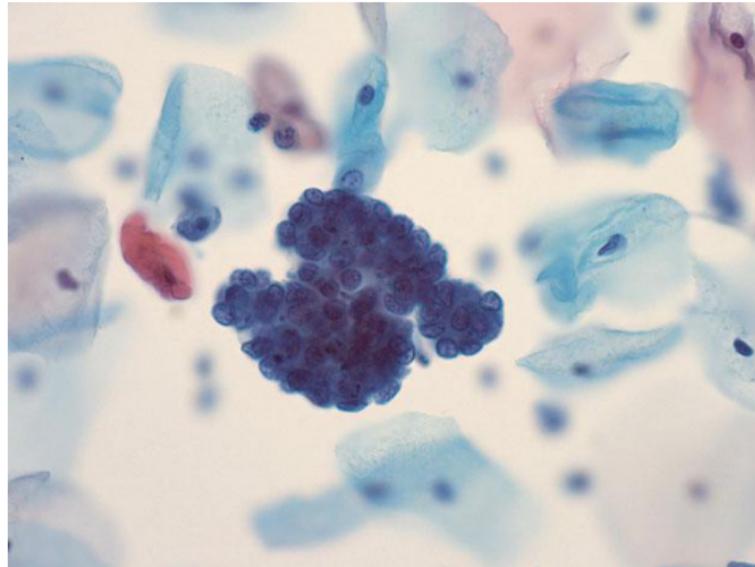
The cytoplasm is dense relative to the intermediate cell, because the intermediate cell cytoplasm flattens out next to the nucleus, whereas in the parabasal cell, the cytoplasm is heaped up.

Endocervical Cell



typical “honeycomb” arrangement

Endometrial Cell



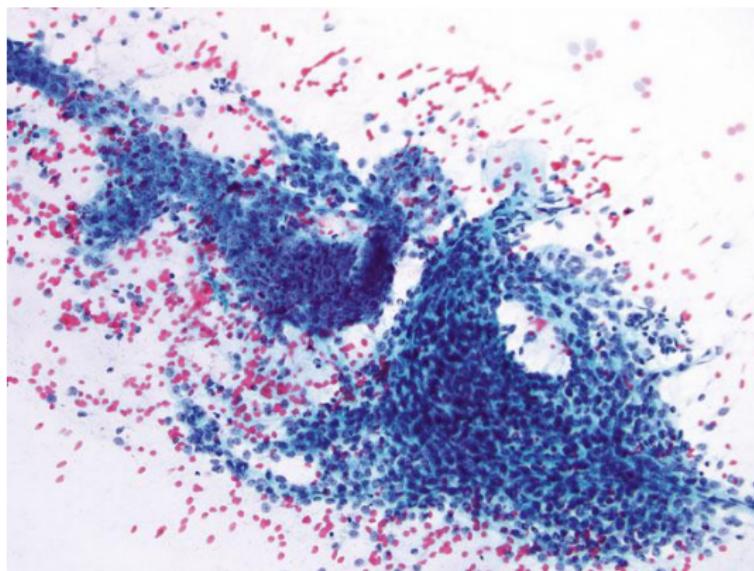
Endometrial cell nuclear to cytoplasmic ratios are high and the cells tend to form three-dimensional groups.

Endometrial cells, exodus (LBP , ThinPrep)



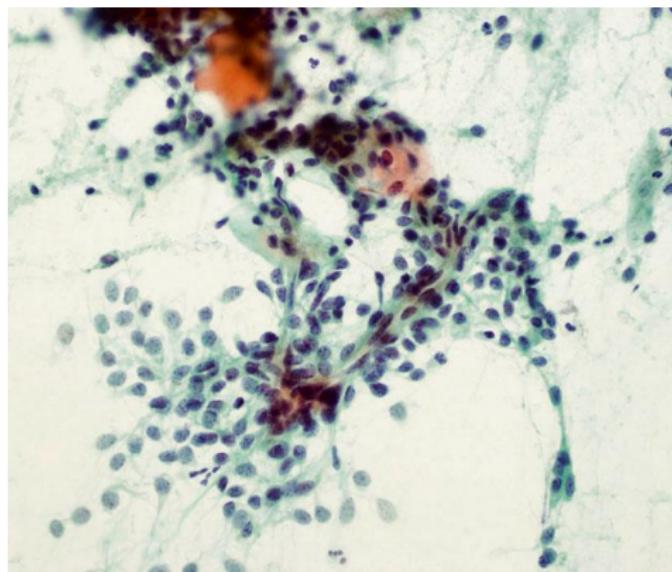
Collections of peripheral glandular and central stromal endometrial cells (exodus ball) are typically seen between day 6 and 10 of the menstrual cycle.

Lower Uterine Segment and Directly Sampled Endometrial Cells



Lower uterine segment sampling with ill-defined glandular cells near the upper left aspect and stromal cells loosely adherent to the glandular cells.

Lower Uterine Segment and Directly Sampled Endometrial Cells

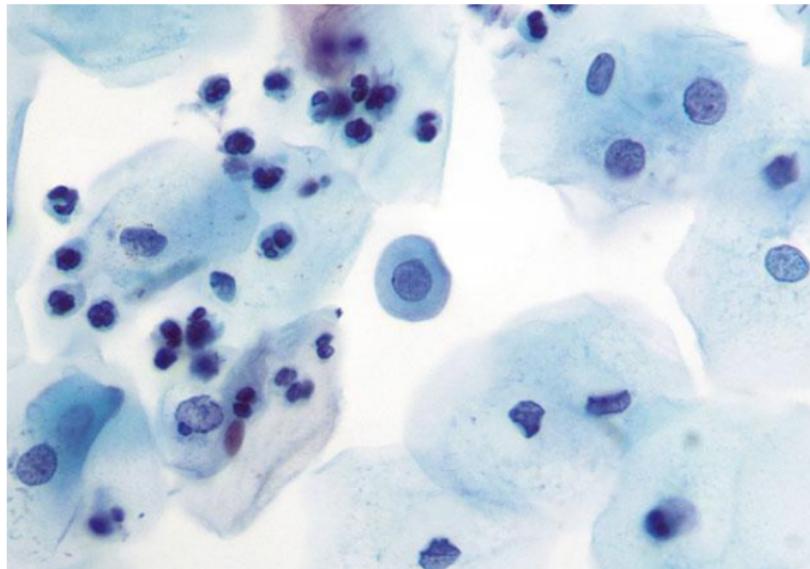


Lower uterine segment sampling (CP). Endometrial stromal cells adherent to blood vessels and flattened against the slide in a fanlike pattern.

Nonneoplastic Cellular Variations

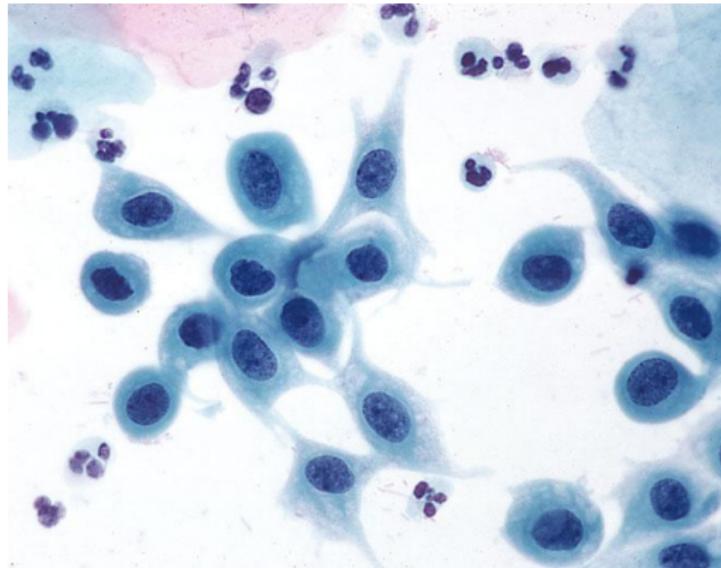
- ▶ Non-neoplastic cellular variations
- ▶ Squamous metaplasia
- ▶ Keratotic changes
- ▶ Tubal metaplasia
- ▶ Atrophy
- ▶ Pregnancy-associated changes

Squamous metaplasia (LBP , SurePath)



The nucleus is round to oval with fine, evenly distributed chromatin.
The nuclear to cytoplasmic ratio is variable

Squamous metaplasia (CP)



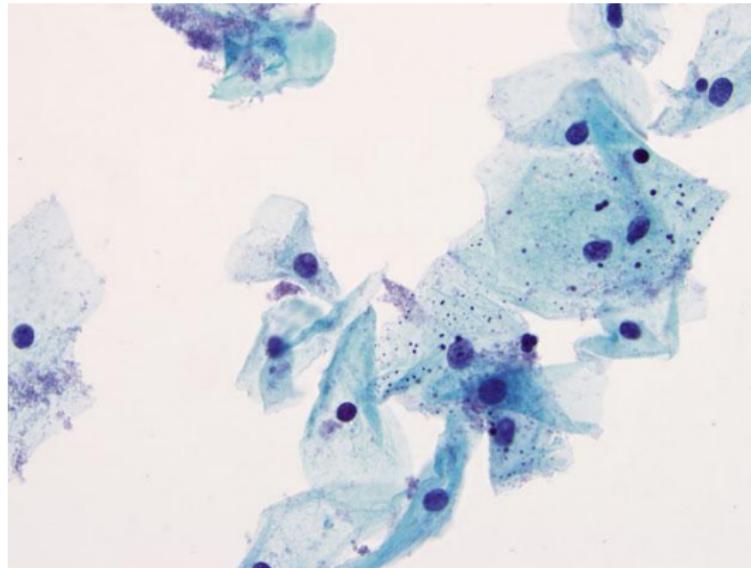
"spidery" cytoplasmic processes, a feature that is seen more often in conventional smears

Squamous metaplasia (CP)



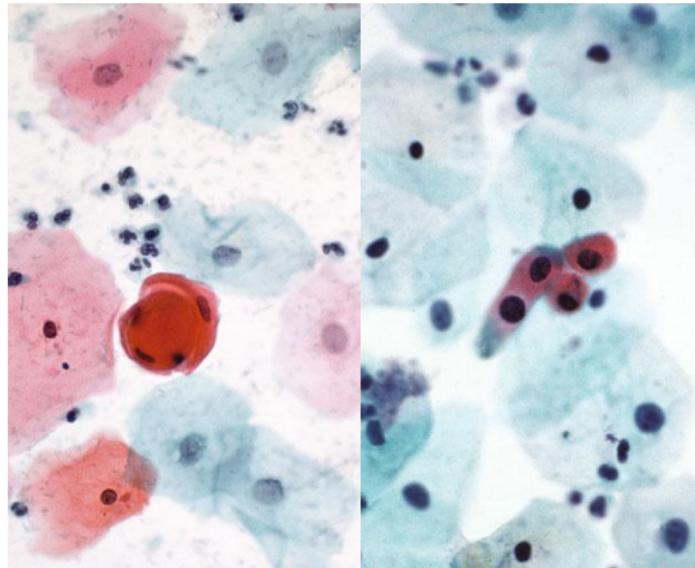
some modest nucleolar prominence that is consistent with reactive/reparative changes

Keratotic cellular changes



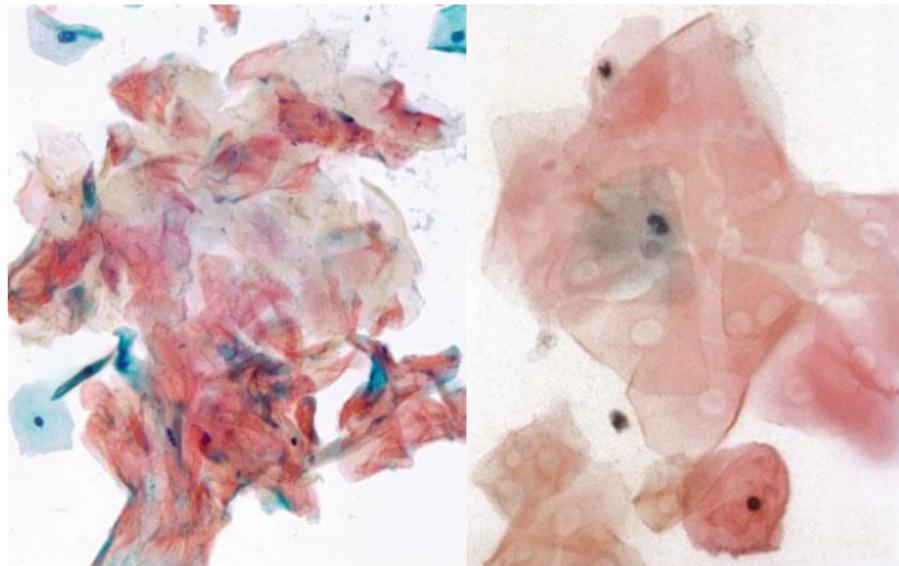
Intermediate squamous cells showing prominent cytoplasmic keratohyaline granules, a precursor to full keratinization

Typical Parakeratosis



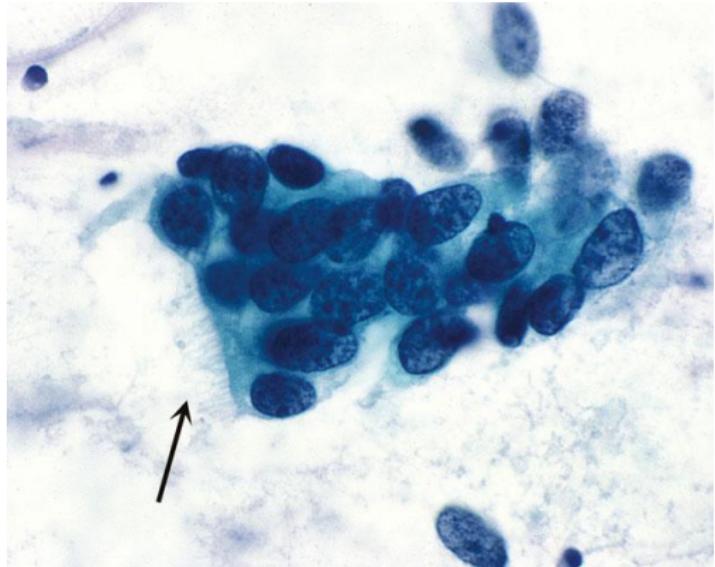
a: "squamous pearl" formation b: small cluster of
miniaturesquamous cells

Hyperkeratosis



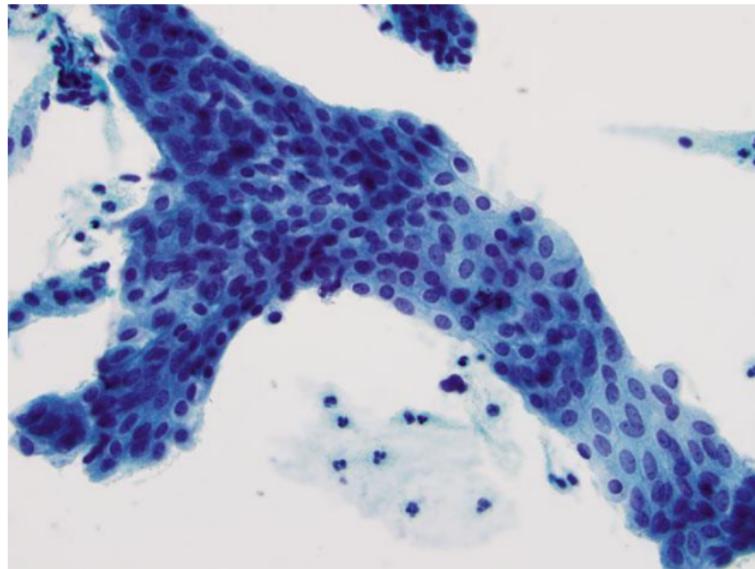
anucleate squames mature polygonal squamous cells with ghostlike
“nuclear holes”

Tubal metaplasia (CP)



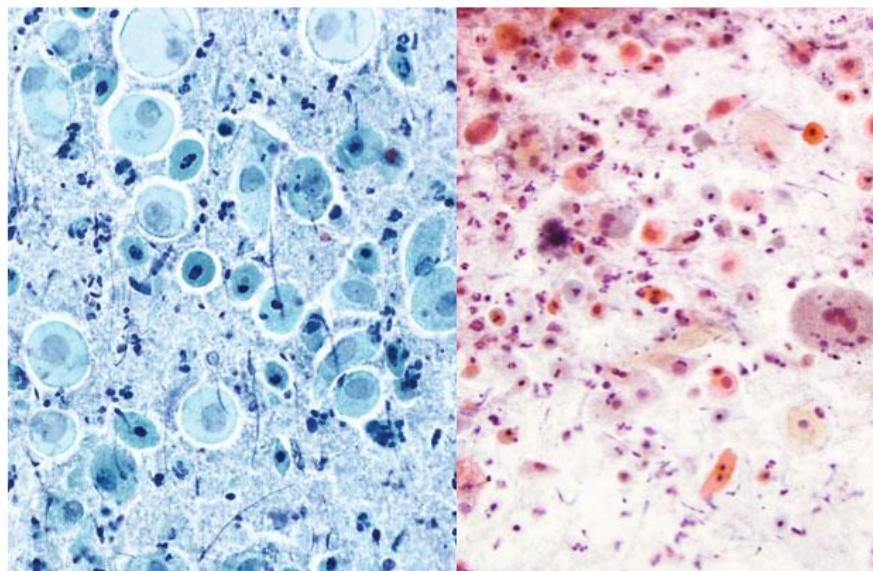
terminal bar and cilia at left edge (arrow) Tubal metaplasia shows prominent pseudostratification

Atrophy



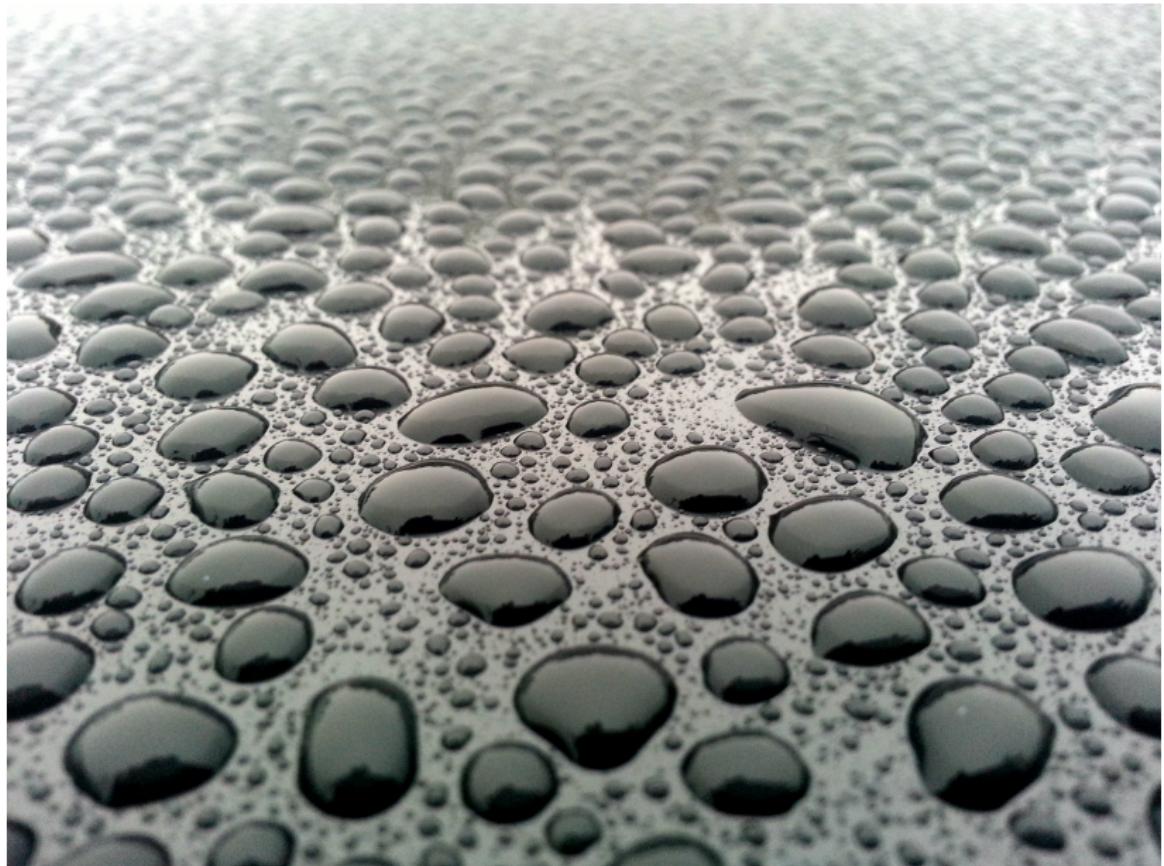
flat, monolayer sheet of parabasal-type cells, with preserved nuclear polarity

Atrophy with inflammation (atrophic vaginitis)

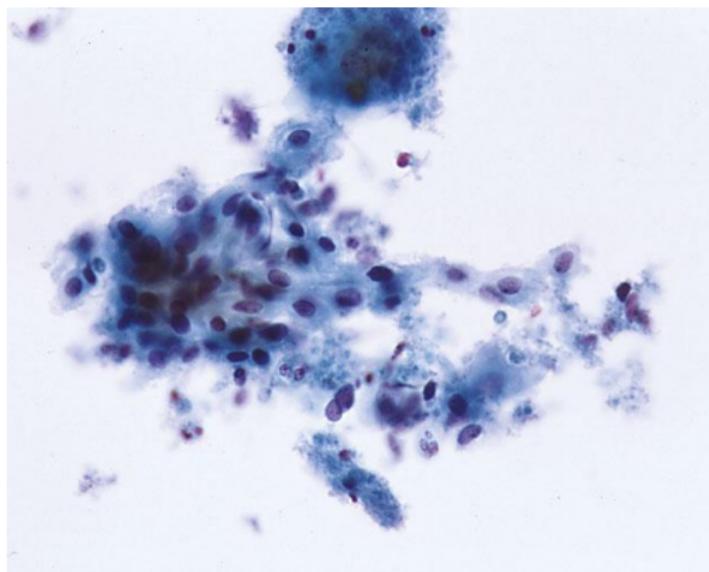


“Blue blobs” and pseudoparakeratosis

Blob

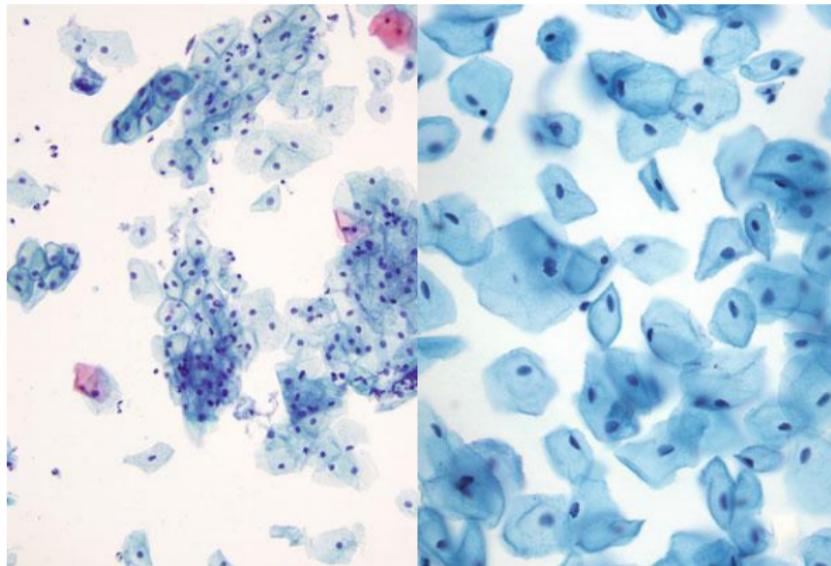


Atrophy with inflammation (atrophic vaginitis)



mimic “clinging tumor diathesis”

Hormonal Changes



In pregnant patients, squamous cells become laden with glycogen, and have a vaguely “boatlike” shape referred to as “navicular” cells

Boatlike, Navicular



NON-NEOPLASTIC FINDINGS

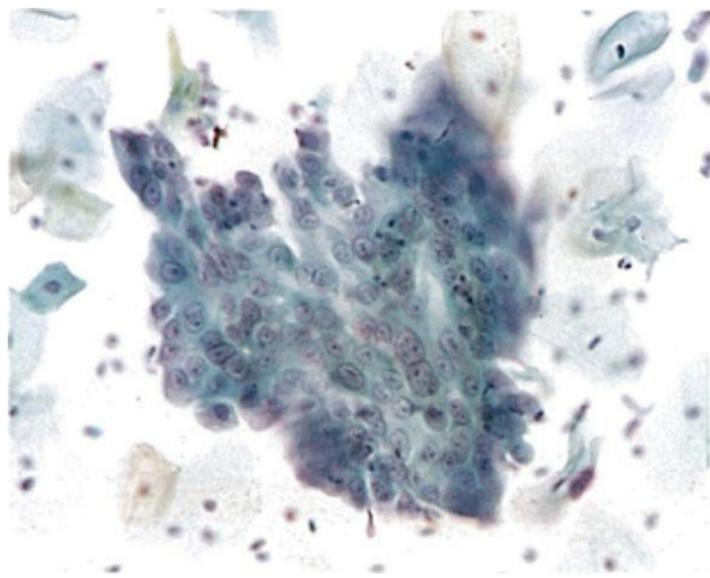
- ▶ Reactive cellular changes associated with:
 - ▶ Inflammation (includes typical repair)
 - ▶ Lymphocytic (follicular) cervicitis
 - ▶ Radiation
 - ▶ Intrauterine contraceptive device (IUD)
 - ▶ Glandular cells status post hysterectomy

Reactive Cellular Changes Associated with Inflammation (Includes Typical Repair)

► Criteria

- ▶ Nuclear enlargement of a variable degree
- ▶ Nuclei are **typically nonoverlapping**
- ▶ Endocervical cells may show greater nuclear enlargement
- ▶ Occasional binucleation or multinucleation may be observed
- ▶ **Nuclear outlines are smooth, round, and uniform**
- ▶ Nuclei may appear **vesicular and hypochromatic**
- ▶ Mild hyperchromasia may be present, but the **chromatin** structure and distribution remain **uniformly finely granular**
- ▶ Prominent single or multiple **nucleoli** may be present
- ▶ Cytoplasmic boundaries are well defined
- ▶ Cytoplasm may show polychromasia, vacuolization, or perinuclear halos but without peripheral thickening
- ▶ Enlarged cells often form cohesive sheets that interdigitate in a classic “school of fish” architecture or may be mechanically distorted by sampling and elongate to form “taffy pull” cytoplasmic appendages

Reactive-reparative cellular changes: reactive endocervical cells (LBP , SurePath)

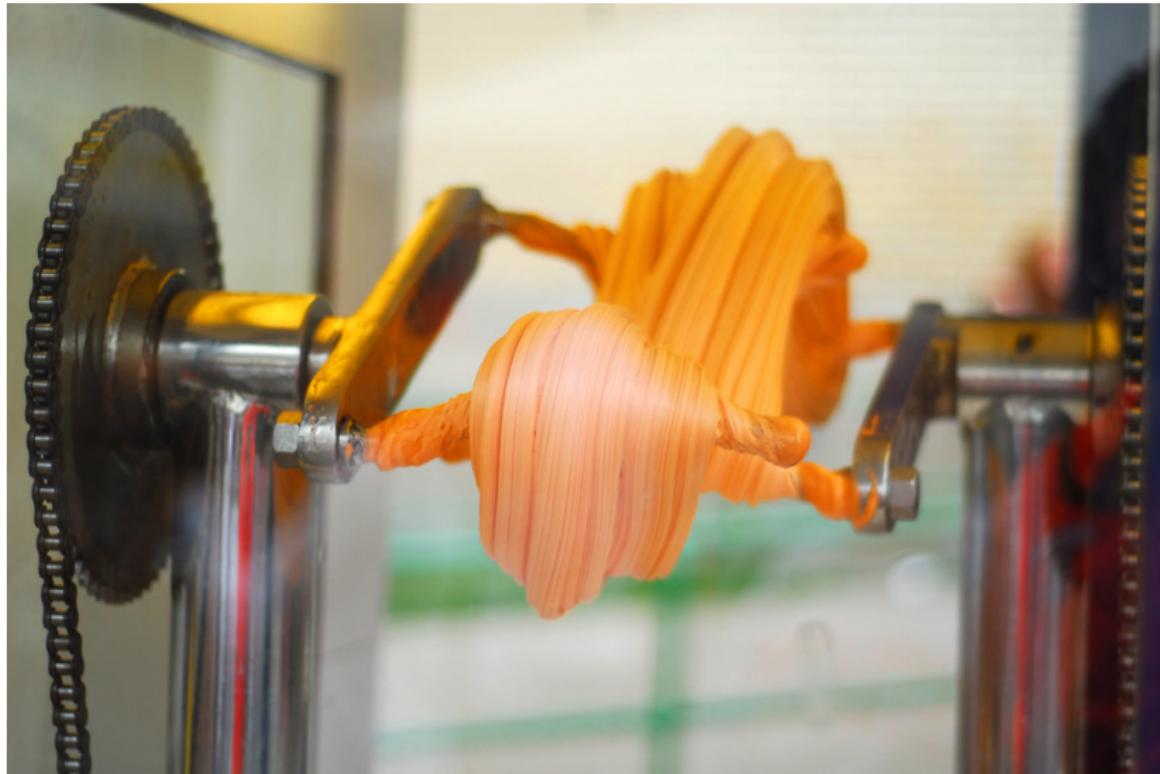


Variation in nuclear size, **prominent nucleoli**, and rare intracytoplasmic polymorphonuclear leukocytes

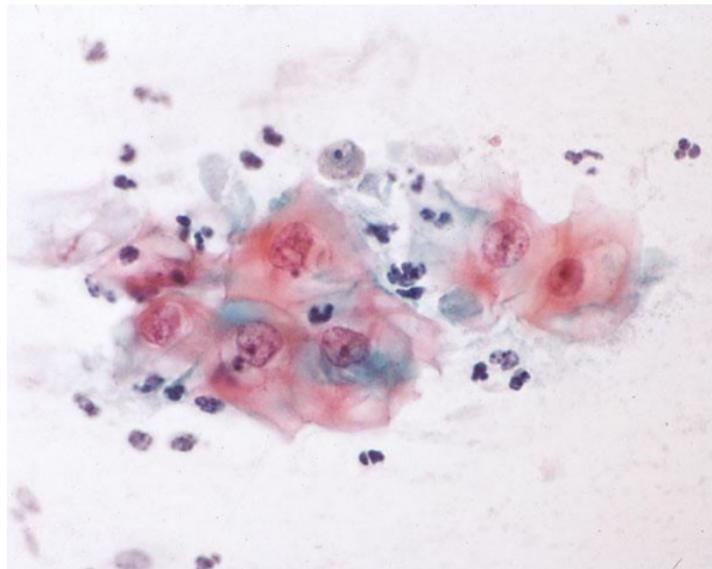
School of fish



Taffy pool

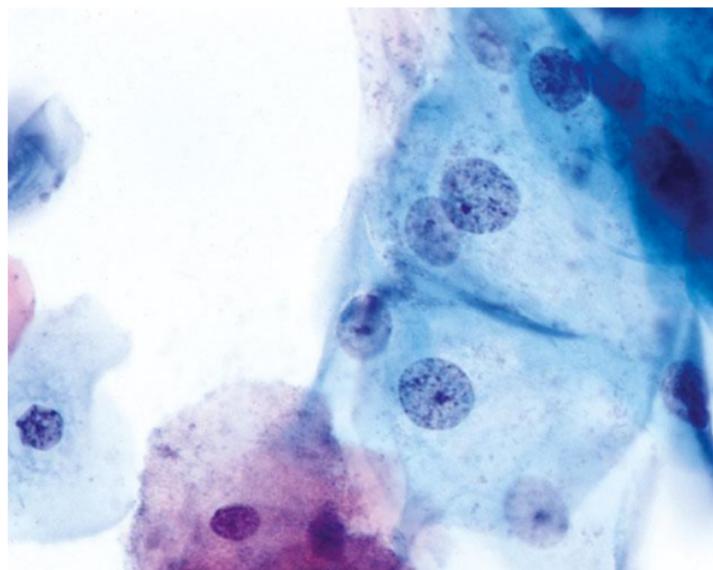


Reactive-reparative cellular changes



mild nuclear enlargement with nuclear hypochromasia, perinuclear halos, and cytoplasmic polychromasia resulting in a "**moth-eaten**" appearance.

Reactive-reparative cellular changes

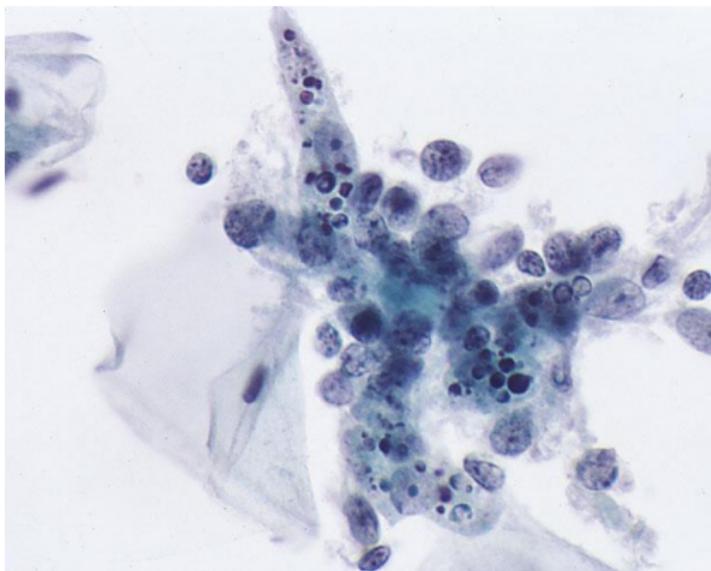


Although there is nuclear enlargement in the cells on the right side, the **smooth nuclear contours** and **finely distributed chromatin** favor reactive change over ASC-US

Lymphocytic (Follicular) Cervicitis

- ▶ Criteria
 - ▶ Polymorphous population of lymphocytes with or without tingible body macrophages

Reactive-reparative cellular changes: lymphocytic (follicular) cervicitis

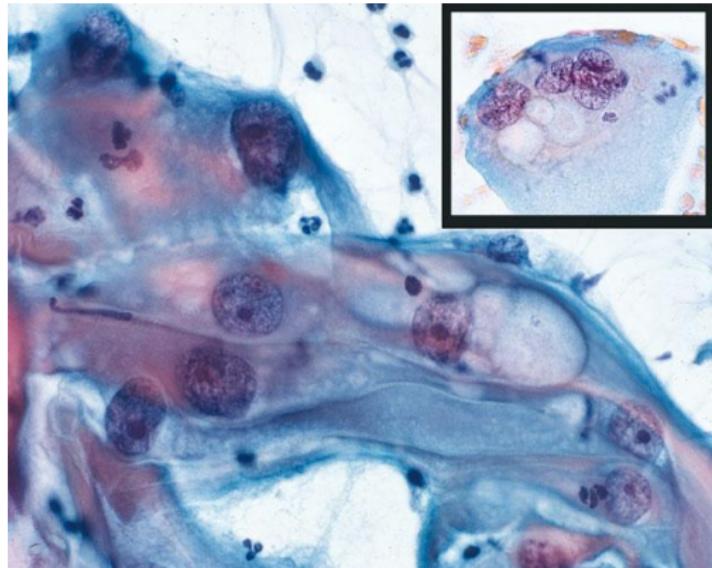


polymorphous population of **lymphoid cells** and tingible body macrophages

Reactive Cellular Changes Associated with Radiation

- ▶ Criteria
 - ▶ Cell size is markedly increased without a substantial increase in the nuclear to cytoplasmic ratio
 - ▶ Bizarre cell shapes may occur
 - ▶ Nuclei may vary in size, with some cell groups having both enlarged and normalsized nuclei
 - ▶ Binucleation or multinucleation is common
 - ▶ Mild nuclear hyperchromasia may be present
 - ▶ Enlarged nuclei may show **degenerative changes** including nuclear pallor, wrinkling or smudging of the chromatin, and nuclear vacuolization
 - ▶ Prominent single or multiple nucleoli may be seen if coexisting repair is present
 - ▶ **Cytoplasmic vacuolization** and/or cytoplasmic polychromatric (two-color, amphophilic) staining and intracytoplasmic polymorphonuclear leukocytes may be seen

Reactive-reparative cellular changes: radiation (CP)



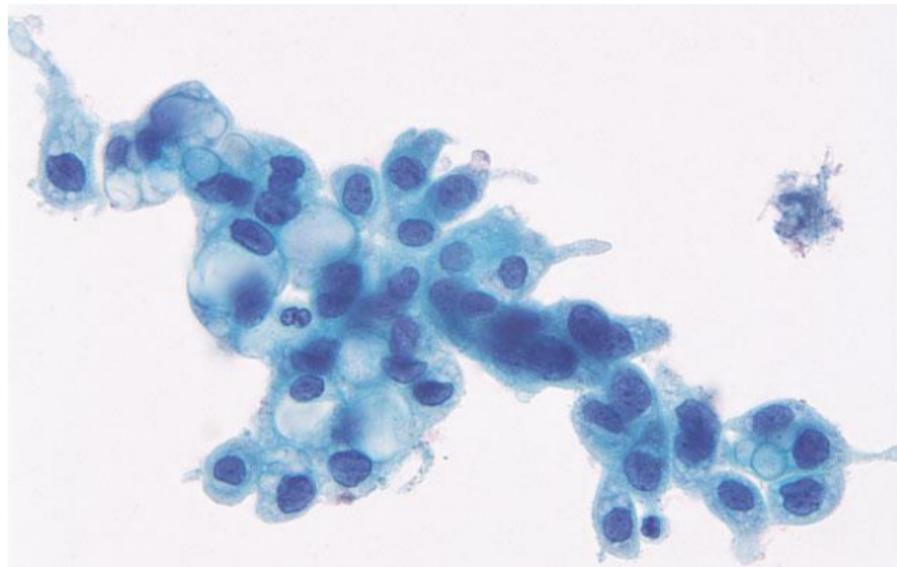
Cells with enlarged nuclei, abundant **vacuolated polychromatic cytoplasm**, mild nuclear hyperchromasia without coarse chromatin, and prominent nucleoli. Note multinucleation (upper right corner inset)

Reactive Cellular Changes Associated with Intrauterine Contraceptive Device

► Criteria

- ▶ Glandular cells may be present singly or in clusters, usually of 5–15 cells, present in a clean background
- ▶ The amount of cytoplasm varies, and frequently **large vacuoles** may displace the nucleus, creating a signet-ring appearance
- ▶ Occasional single epithelial cells with increased nuclear size and high nuclear to cytoplasmic ratio may be present, which can be mistaken for HSIL/ASC-H
- ▶ Nuclear degeneration with a “wrinkled” chromatin appearance or nuclear “cracking” may be present
- ▶ Nucleoli may be prominent
- ▶ Calcifications resembling psammoma bodies are sometimes present
- ▶ Actinomyces-like organisms may be present in up to 25 % of cases

Reactive- reparative cellular changes: IUD (LBP , Thin Prep)



small cluster of glandular cells with **cytoplasmic vacuoles** displacing nuclei

ORGANISMS

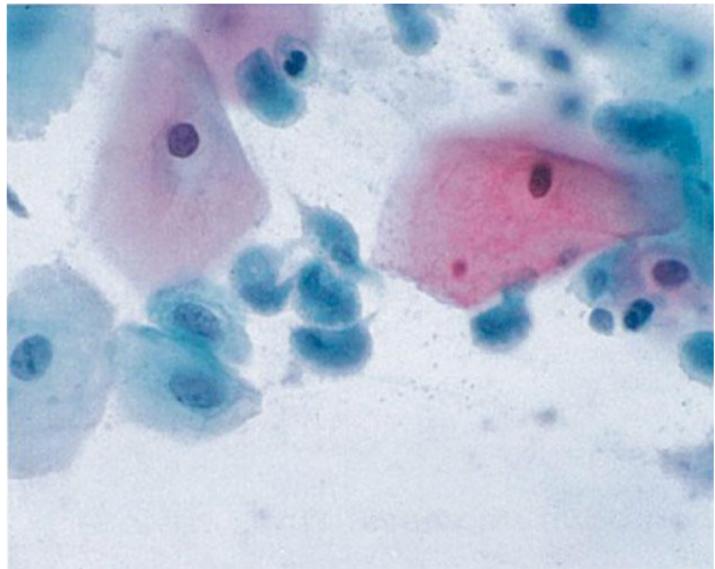
- ▶ *Trichomonas vaginalis*
- ▶ Fungal organisms morphologically consistent with *Candida* spp.
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- ▶ Bacteria morphologically consistent with *Actinomyces* spp.
- ▶ Cellular changes consistent with herpes simplex virus
- ▶ Cellular changes consistent with cytomegalovirus

Trichomonas vaginalis

► Criteria

- ▶ Pear-shaped, oval, or round cyanophilic organism ranging in area from 15 to 30 μm^2
- ▶ Nucleus is pale, vesicular, and eccentrically located
- ▶ **Eosinophilic cytoplasmic granules** are often evident
- ▶ Flagella are sometimes observed
- ▶ Leptothrix may be seen in association with *T. vaginalis*
- ▶ Associated background changes include mature squamous cells with small perinuclear halos ("trich change") and 3-dimensional clusters of neutrophils ("polyballs")

Trichomonas vaginalis

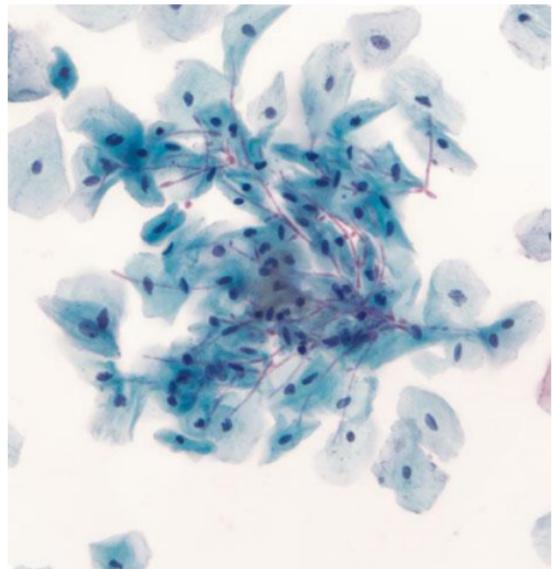


trichomonads. Pear-shaped organism with eccentrically located nucleus and eosinophilic cytoplasmic granules. Presence of a **nucleus and cytoplasmic granules** distinguishes trichomonads from cytoplasmic fragments

Fungal Organisms Morphologically Consistent with *Candida* Species

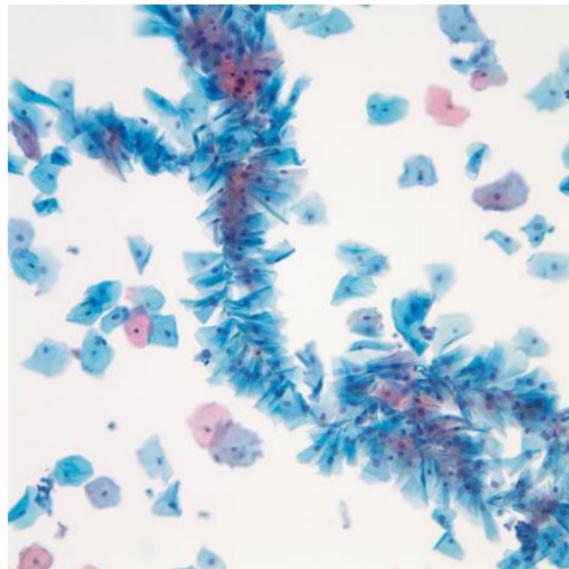
- ▶ Criteria
 - ▶ Budding yeast (3–7 um) and/or **pseudohyphae**; pseudohyphae can be quite long, spanning many cells, and are eosinophilic to gray brown on the Papanicolaou stain
 - ▶ Pseudohyphae, formed by cytoplasmic extension of **budding yeasts**, lack true septations but show complete constrictions along their length that indicate the formation of new cells
 - ▶ Fragmented leukocyte nuclei and groups of squamous epithelial cells “speared” by pseudohyphae and held together in a rouleaux are often seen

Candida species



pseudohyphae and modest number of yeast forms

Candida species



“spearing” or a “shish kebab” appearance of squamous cells. This feature is readily appreciated at low power, even when the pseudohyphae are not prominent.

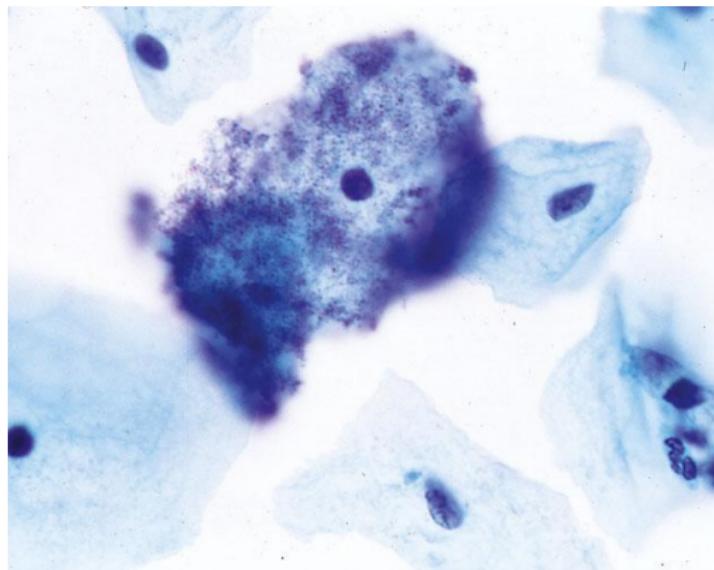
Shish kebab



Shift in Flora Suggestive of Bacterial Vaginosis

- ▶ Criteria
 - ▶ Individual squamous cells are covered by a layer of coccobacilli that obscure the cell membrane, forming the so-called clue cells
 - ▶ Large numbers of inflammatory cells indicate a vaginitis rather than a vaginosis. There is a conspicuous absence of lactobacilli

Bacteria – coccobacilli

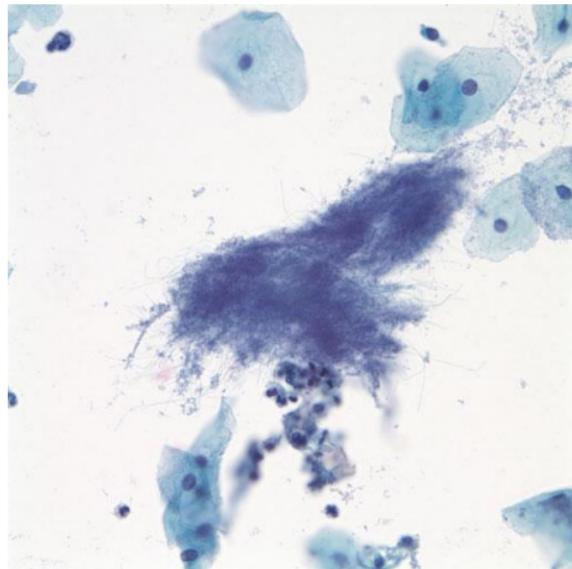


"clue cell"

Bacteria Morphologically Consistent with Actinomyces

- ▶ Criteria
 - ▶ Tangled clumps of filamentous organisms, often with acute angle branching, are recognizable as “cotton ball” clusters on low power
 - ▶ Filaments sometimes have a radial distribution or have an irregular “woolly body” appearance
 - ▶ Masses of leukocytes adherent to microcolonies of the organism with swollen filaments or “clubs” at the periphery may be identified
 - ▶ An acute inflammatory response with polymorphonuclear leukocytes is often present

Bacteria morphologically consistent with Actinomyces

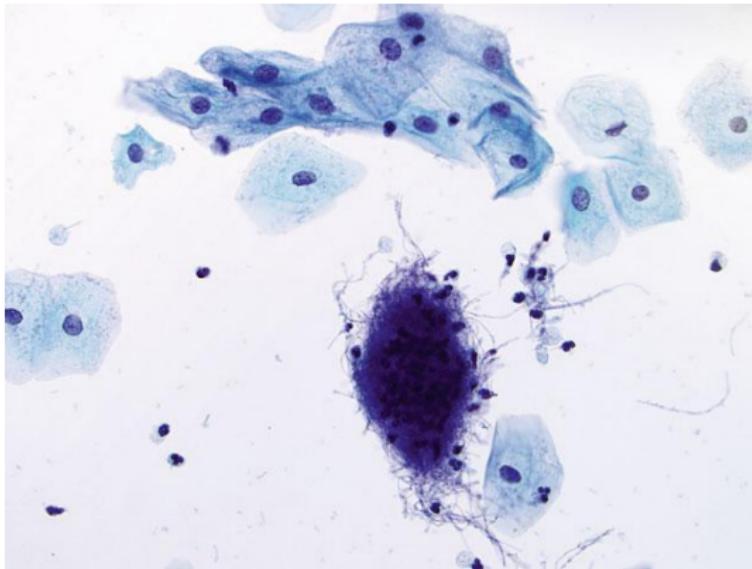


“cotton ball” appearance of tangled clumps of filamentous organisms.

Cotton ball



Bacteria: *lactobacilli* (LBP , ThinPrep)



lactobacilli may aggregate to form “clumps” that may **resemble** ***Actinomyces*** species and should be distinguished by the presence of similar isolated bacilli in the background and absence of characteristic features of actinomyces

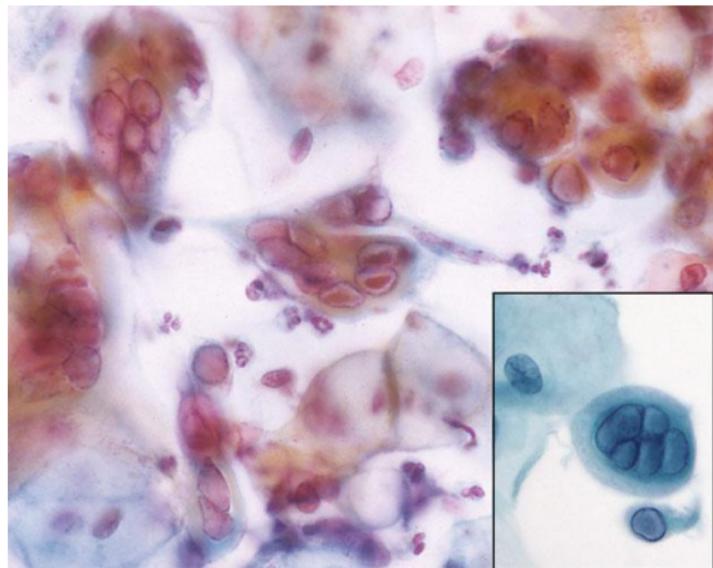
Clumps



Cellular Changes Consistent with Herpes Simplex Virus

- ▶ Criteria
 - ▶ Nuclei have a “ground-glass” appearance due to intranuclear viral particles and enhancement of the nuclear envelope caused by peripheral margination of chromatin
 - ▶ Dense eosinophilic intranuclear (Cowdry) inclusions surrounded by a halo or clear zone are variably present and can be seen in both primary and recurrent infections
 - ▶ Large multinucleated epithelial cells with molded nuclei are characteristic but may not always be present; mononucleate cells with the nuclear features described above may be the only finding

Cellular changes consistent with herpes simplex virus



eosinophilic intranuclear “Cowdry A-type” inclusions. The “ground-glass” appearance of the nuclei is due to accumulation of viral particles leading to peripheral margination of chromatin

OTHER

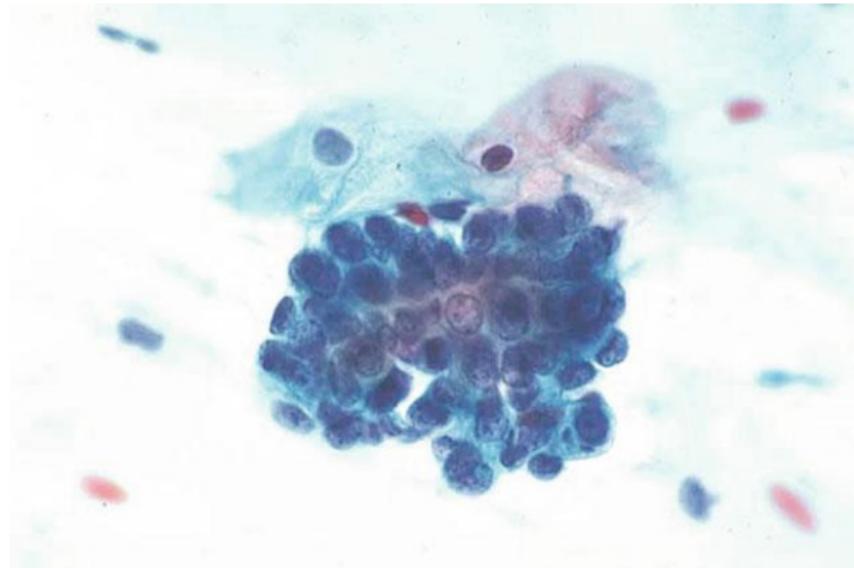
- ▶ Endometrial cells (in a woman ≥ 45 years of age)
(Specify if “negative for squamous intraepithelial lesion”)

Exfoliated Endometrial Cells

► Criteria

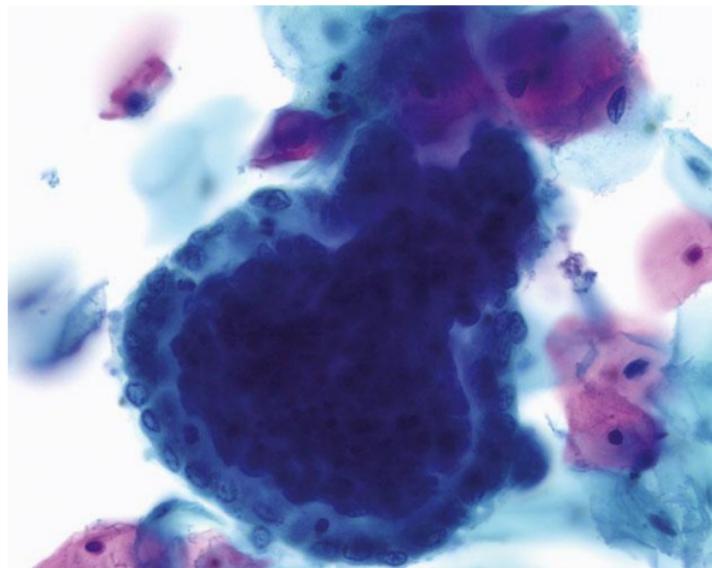
- ▶ Cells are small and often arranged in tight, ball-like clusters, rarely as isolated cells
- ▶ Nuclei are small, similar in area to a normal intermediate squamous cell nucleus
- ▶ Some nuclei around the edge of clusters may have a cup-shaped appearance
- ▶ Nuclei are dark, but the chromatin pattern is often difficult to discern because of overlapping cells
- ▶ Nucleoli are inconspicuous
- ▶ Karyorrhexis is often present
- ▶ Mitoses are absent
- ▶ Cytoplasm is scant, occasionally vacuolated
- ▶ Cell borders are ill defined
- ▶ Double-contoured clusters of endometrial cells may be seen
- ▶ Nucleoli and chromatin detail may be more apparent; intracytoplasmic vacuoles are more common and easily visible
- ▶ Karyorrhexis is easily seen
- ▶ Background appears cleaner, especially in menstrual smears

Exfoliated endometrial cells



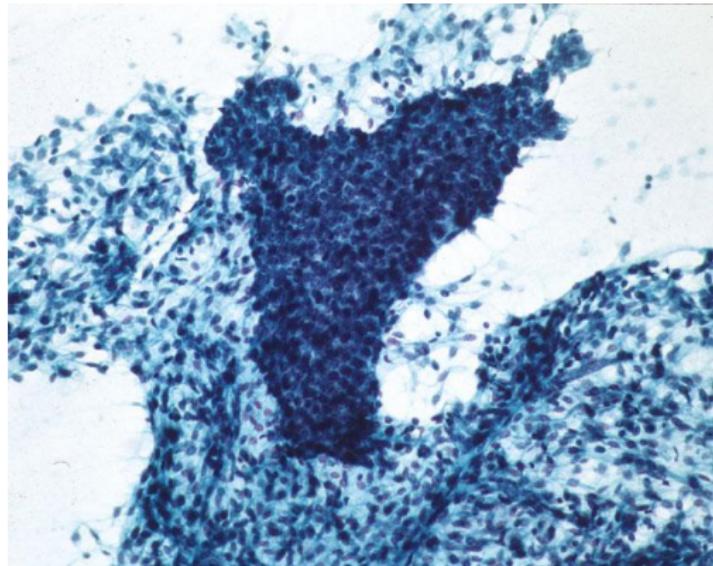
Cells are arranged in three-dimensional clusters. Nuclei are small and similar in size to an intermediate squamous cell nucleus. Nucleoli are inconspicuous. Cytoplasm is scant, and cell borders are indistinct.

Exfoliated endometrial cells



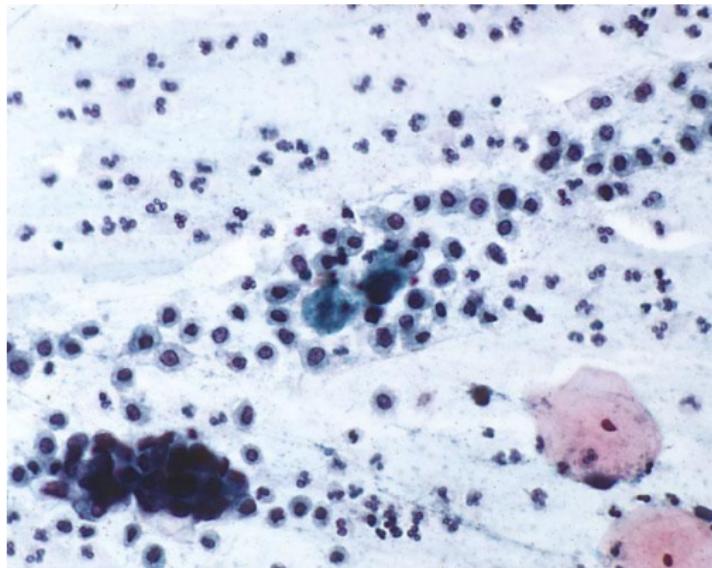
Double-contoured cluster of exfoliated endometrial cells (LBP , ThinPrep). Endometrial glandular cells surround a dark core of stromal cells.

Abraded lower uterine segment (LUS) fragment



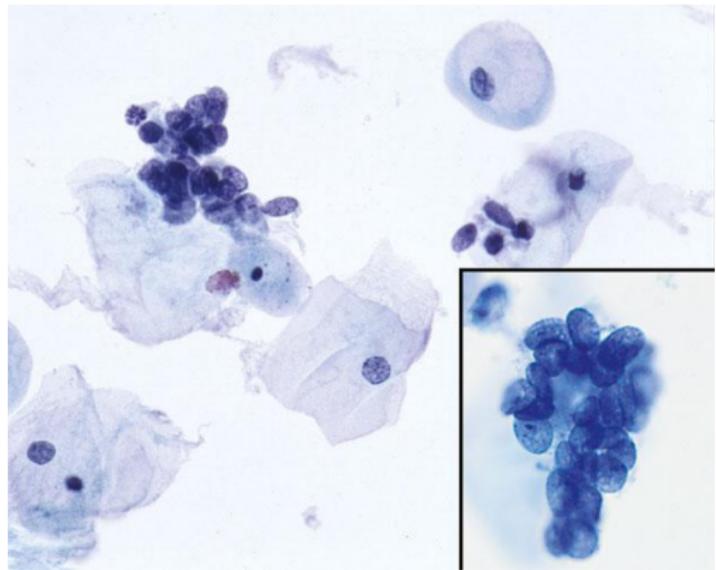
Abraded LUS/endometrium does not carry the same implications as exfoliated endometrial cells

Histiocytes (CP)



Histiocytes have a round to reniform nucleus and a moderate amount of finely vacuolated cytoplasm. They are often seen in association with exfoliated endometrial cells.

“Small blue cells”



Naked nuclei are clustered and demonstrate molding. The insert (lower right) shows a higher magnification of a grapelike cluster of nuclei with finely textured chromatin. Such clusters **should not be mistaken** for endometrial cells