Endometrial Cells and Their Mimics

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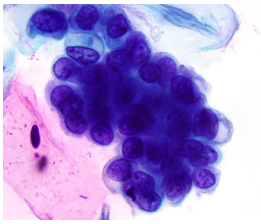
Outline

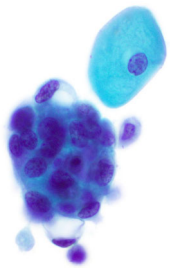
- Benign Endometrial Cells
- Differential Diagnosis
- Bethesda System and Reporting Endometrial Cells
- ASCCP Guidelines

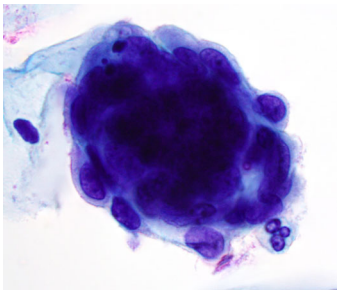
Benign Endometrial Cells

- Spontaneously shed or exfoliated endometrial cells
  - Common during the first 12 days of the menstrual cycle
  - "Out of phase": IUD, endometrial polyp, endometriosis
  - Considered abnormal in post-menopausal women
- Direct sampling – lower uterine segment
  - More common in patients with previous cervical excision (LEEP, cone, etc.)

Exfoliated Endometrial Cells



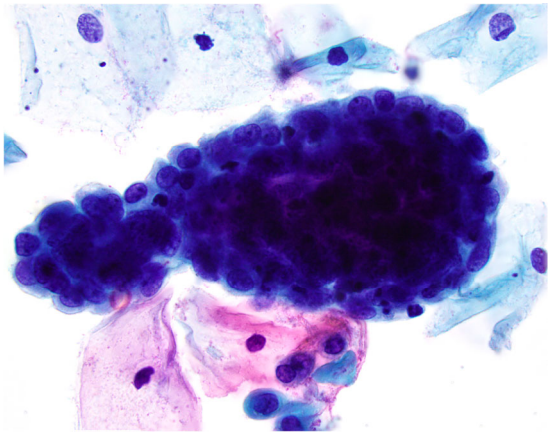


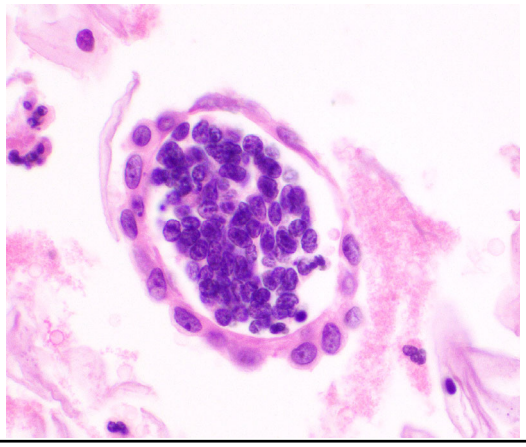


- Small cells with scant cytoplasm and dark nuclei
- Can occur as:
  - Balls or clusters w/scalloped edges
  - Isolated cells
  - Dual cell population
- Cytoplasm typically scant but can be vacuolated
- Poorly-defined cell borders
- Molding
- Apoptotic debris
- No mitoses

Exfoliated Endometrial Cells

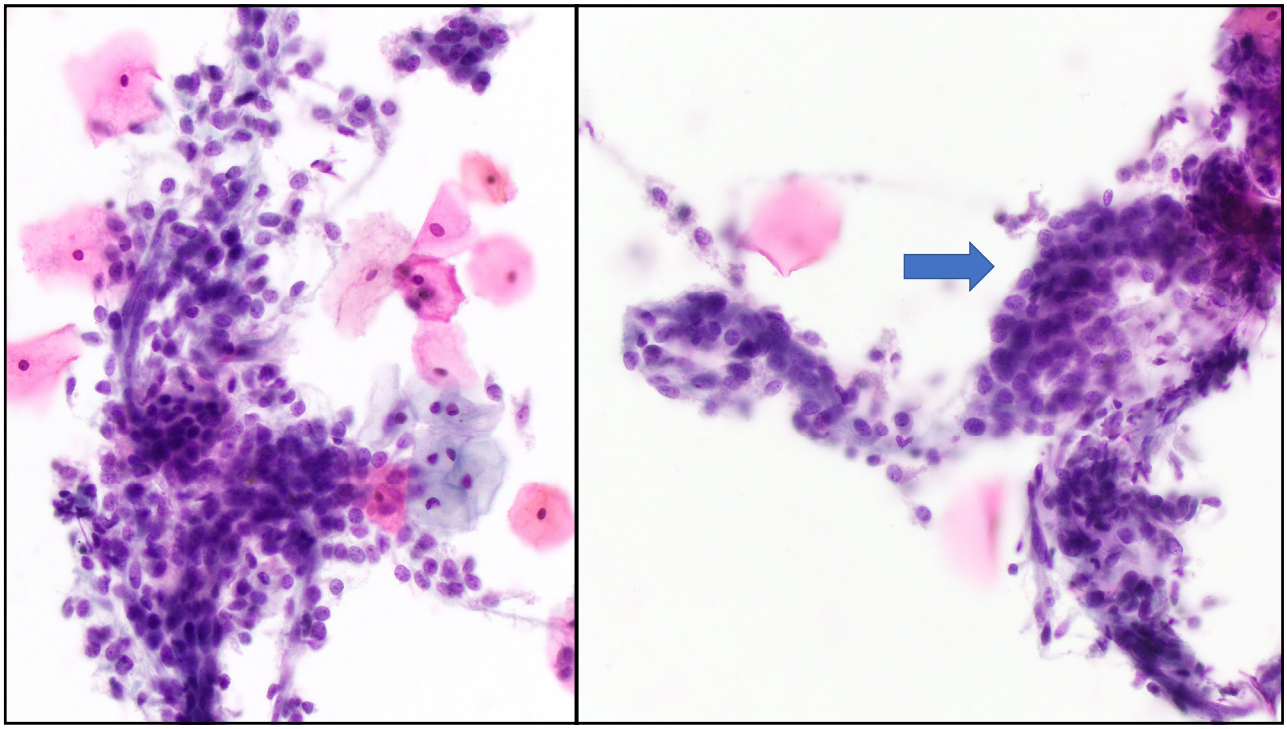
- Clusters show varying amounts of glandular and stromal cells

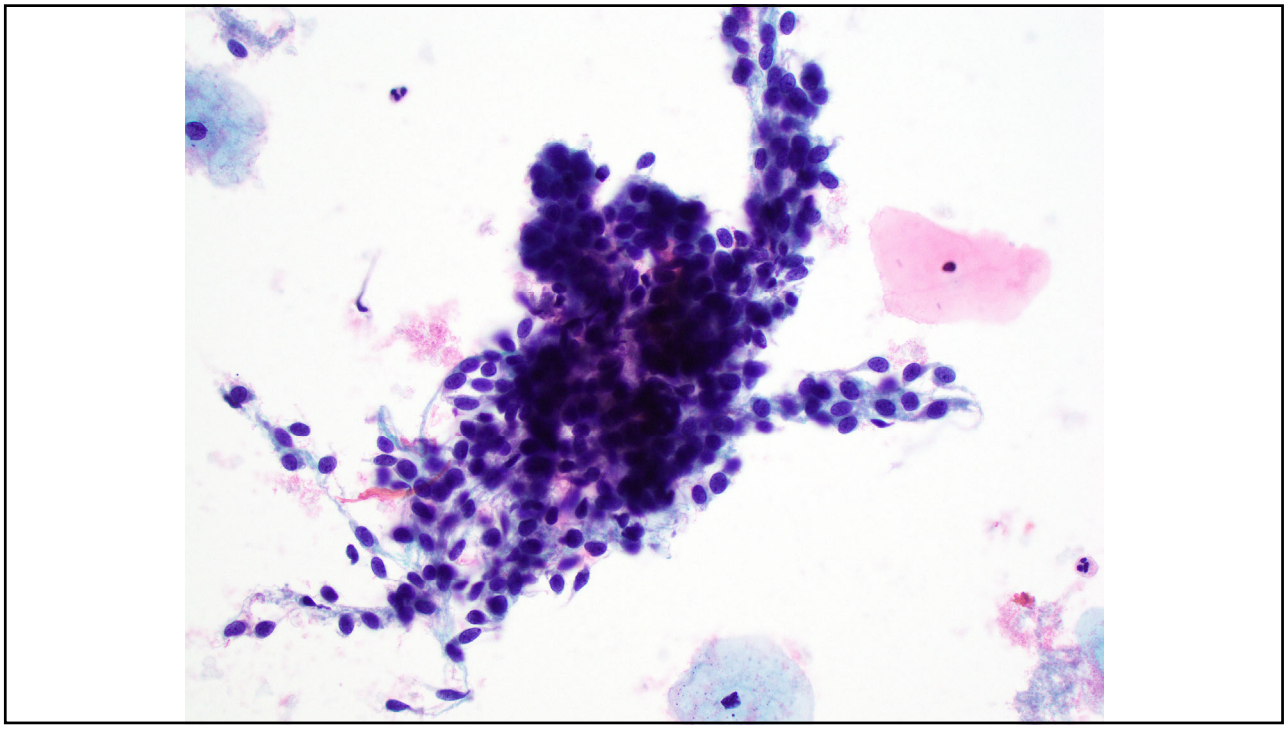


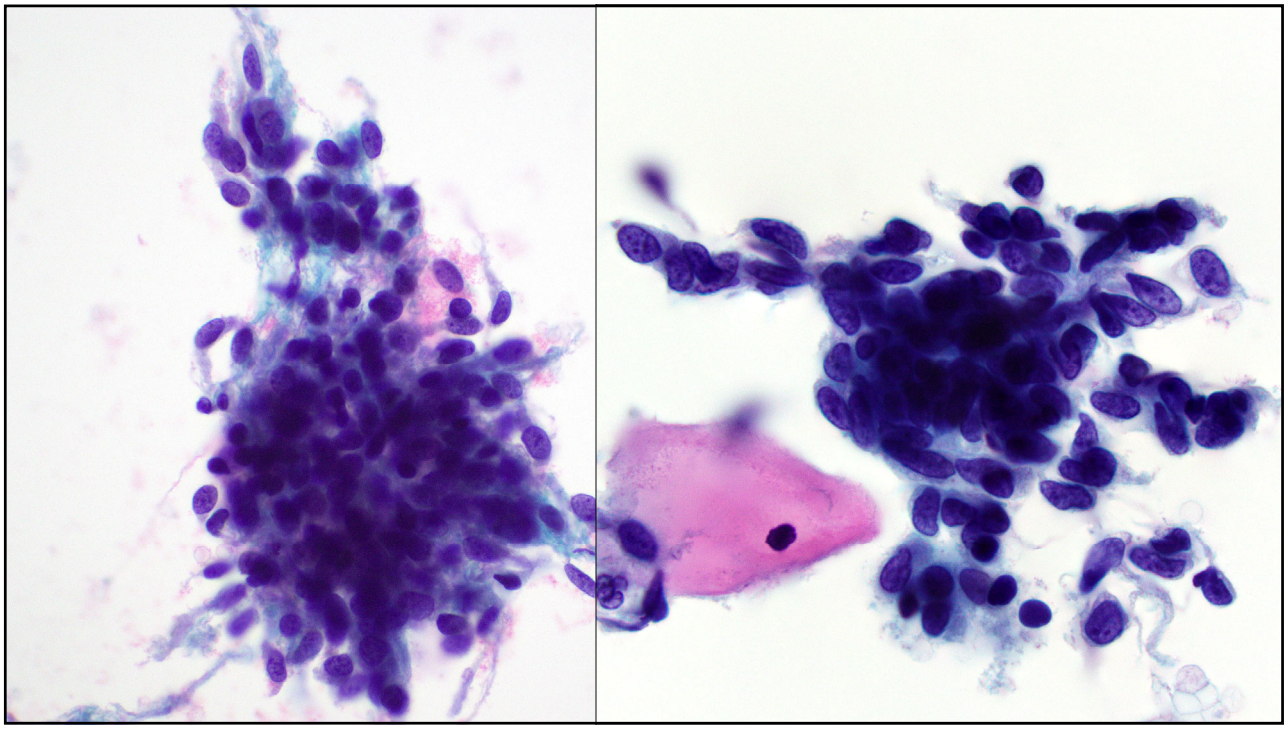


Direct Sampling – Lower Uterine Segment

- Well preserved cellular hyperchromatic groups
- Mix of endometrial and stromal tissue
  - Smaller groups may appear as only glandular or stromal cell
  - Larger groups will typically have glandular cells in sheets or tubules
- Cells (glandular or stromal) are often uniform
- Stroma often manifests as spindled cells associated with glandular groups
- Mitotic activity can be found during proliferative phase







Mimics of Endometrial Cells

Non-neoplastic

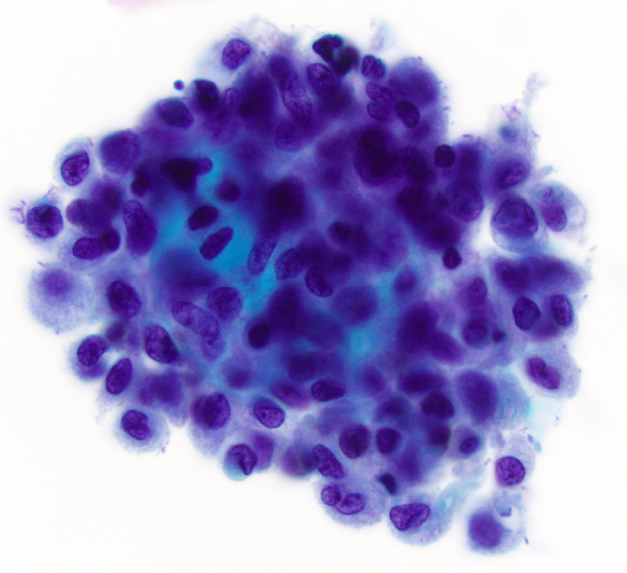
- Histiocytes
- Lymphocytes
- Endocervical cells
- Bare nuclei

Neoplastic

- HSIL
- Squamous cell carcinoma
- Adenocarcinoma *in situ*
- Small cell carcinoma

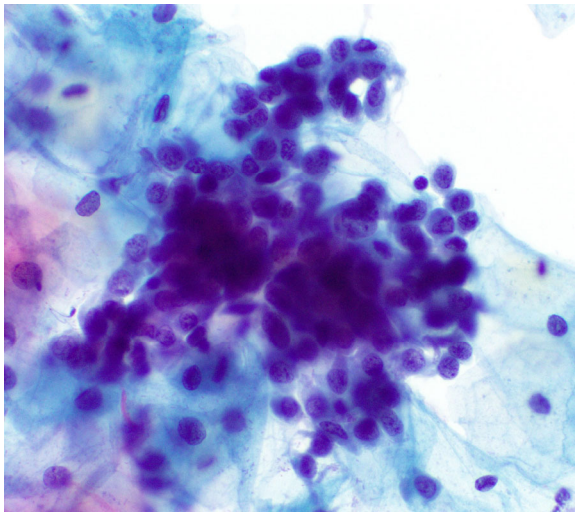
Histiocytes

- Often sparse and typically in dispersed groups
- Distinct nuclear features: kidney bean-shaped or folded nuclei
- Moderate amounts of cytoplasm



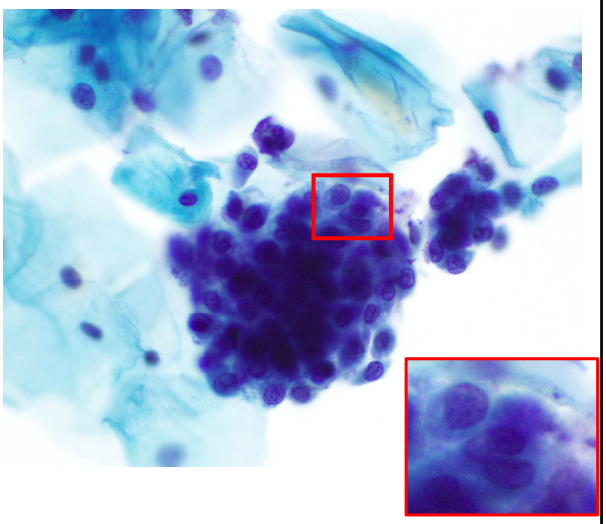
Histiocytes

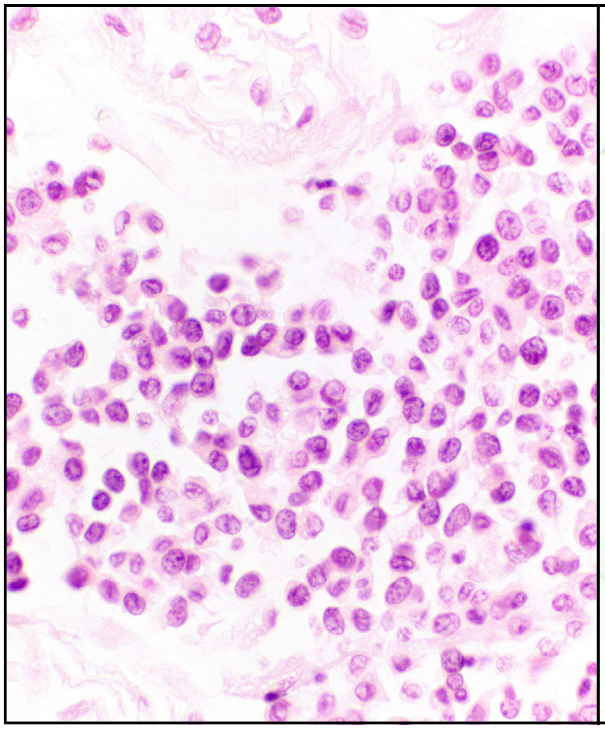
- Often sparse and typically in dispersed groups
- Distinct nuclear features: kidney bean-shaped or folded nuclei
- Moderate amounts of cytoplasm
- Can appear as tight clusters mimicking endometrial cells



Histiocytes

- Similarities to endometrial cells:
  - Can appear in tight clusters of cells with high N:C ratios
- Distinct features:
  - Single cell type
  - Typically dispersed and loose clusters
  - Nuclear features: folded/kidney bean shaped nuclei
  - Moderate amounts of cytoplasm +/- vacuolization





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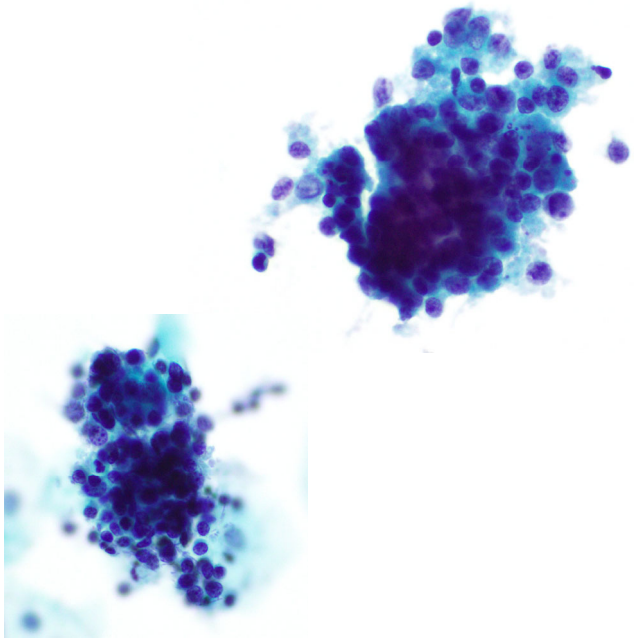
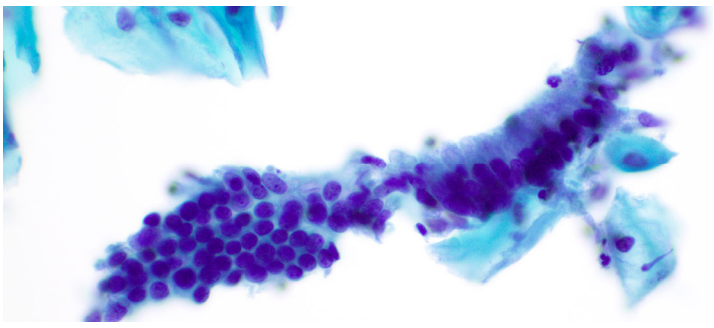
Lymphoid Cells

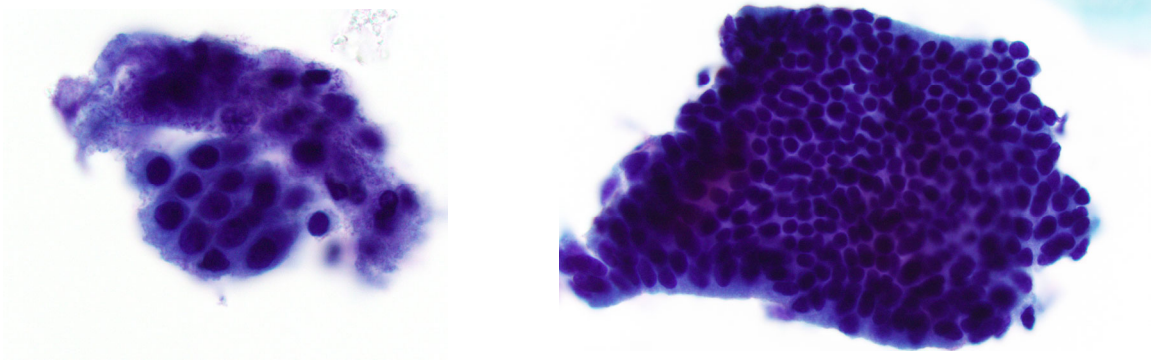
- Aggregates can mimic exfoliated endometrial cells
- Small round lymphocytes often associated with plasma cells or tangible body macrophages



Endocervical Cells

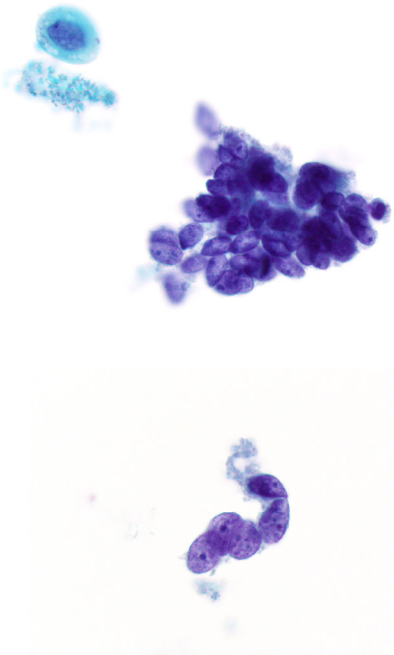
- Typically in sheets or strips
- Honeycomb arrangement
- Atrophic endocervical cells in older patients:
  - Residual columnar shape





Small Bare Nuclei

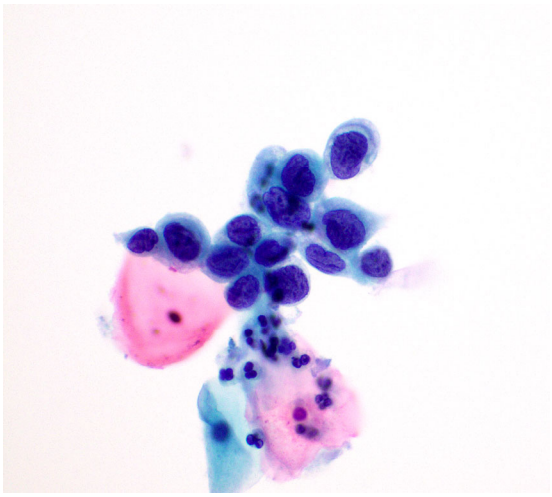
- Clusters of bare squamous nuclei often associated with atrophy
- Similarities to endometrial cells:
  - Can have “scalloped” edges and molding
  - Typically small groups
- Distinct from endometrial cells:
  - Lack cytoplasm
  - Atrophic background
  - Looser and more “irregular” clusters
  - Chromatin evenly distributed
  - Lack of hyperchromasia

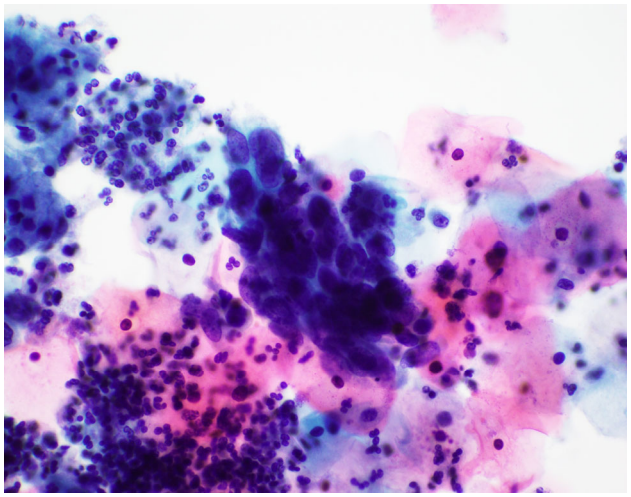


Neoplastic Mimics of Exfoliated Endometrial Cells

- HSIL
- Squamous Cell Carcinoma
- Adenocarcinoma *in situ*
- Small Cell Carcinoma

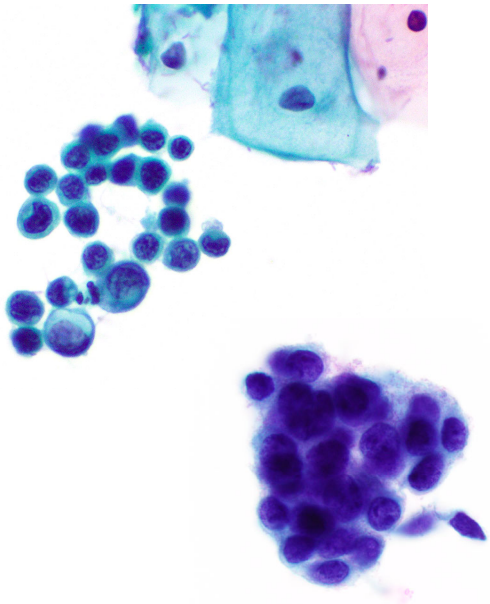
HSIL



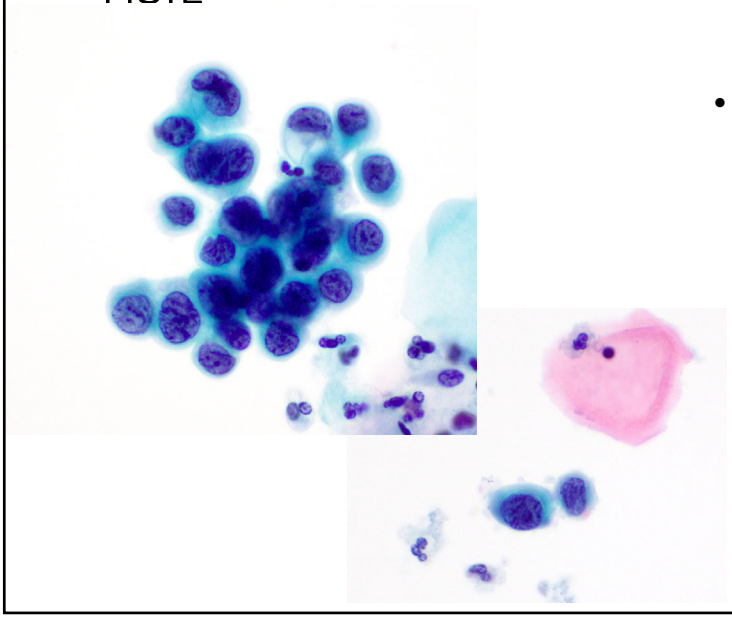


HSIL

- Similarities to endometrial cells:
  - Hyperchromatic groups
  - Crowding
  - High N:C ratios
- A subset of HSILs are made up primarily of “small cells”
- Crowded groups may be difficult to discern from endometrial cells

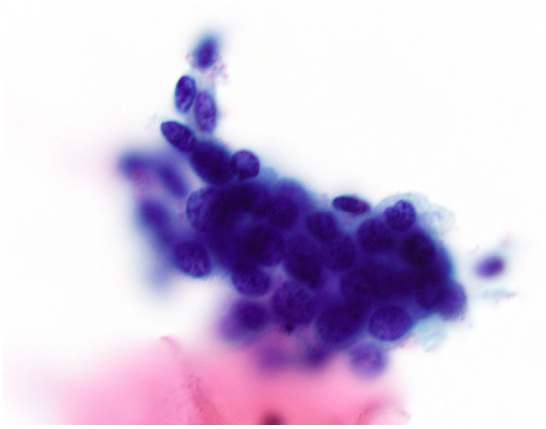


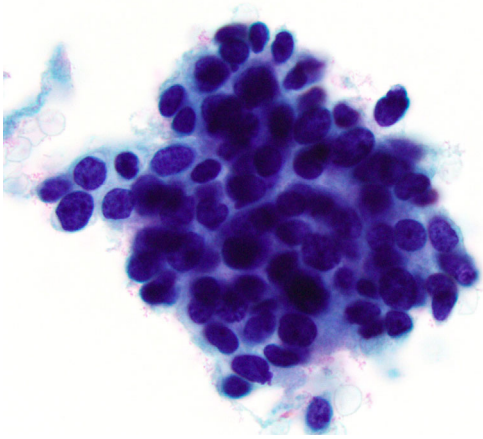
HSIL

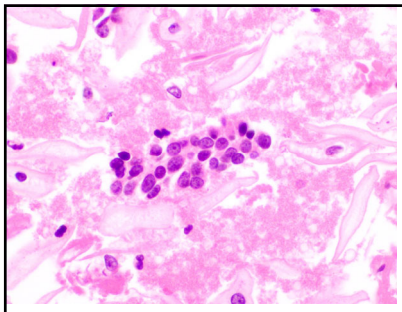


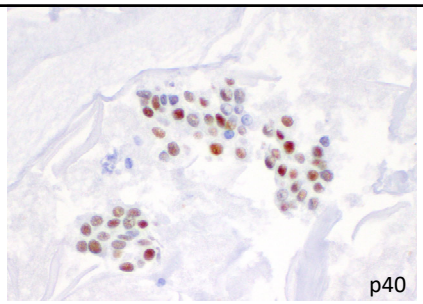
- Features favoring HSIL:
  - Cells typically larger than benign endometrial cells
  - Variation in cell size
  - Flat sheets
  - Spherical groups absent
  - Single dysplastic cells
  - Irregular nuclear contours
  - Mitotic activity
  - HPV test results

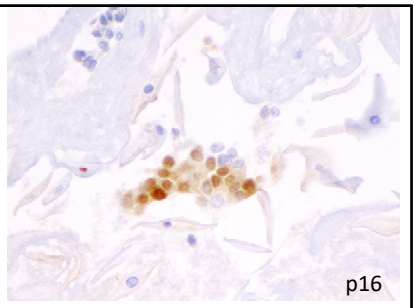
31 y/o with prior HSIL - LMP day 6



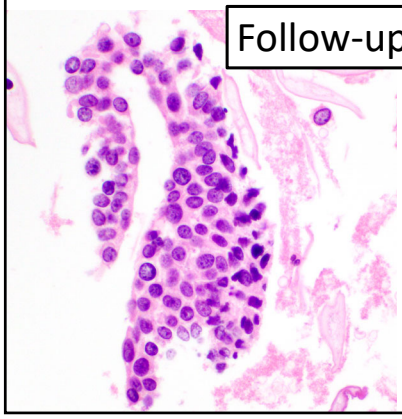


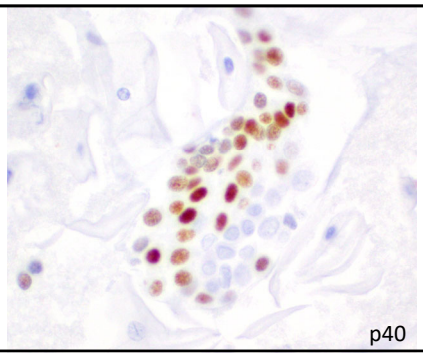


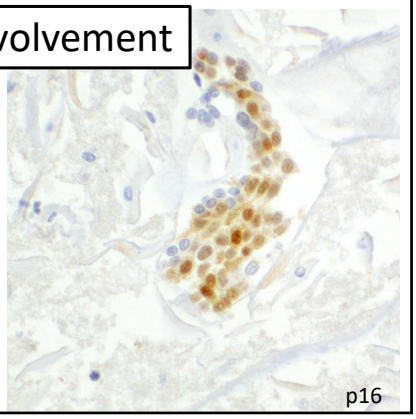




Follow-up Biopsy: HSIL with gland involvement





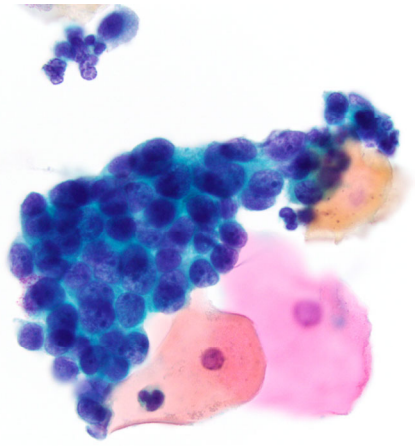


Cautionary Note – Cell Blocks

- Cell blocks derived from Liquid Based Cytology Samples are alcohol fixed.
- Immunohistochemical stains may not have been validated on methanol fixed tissue:

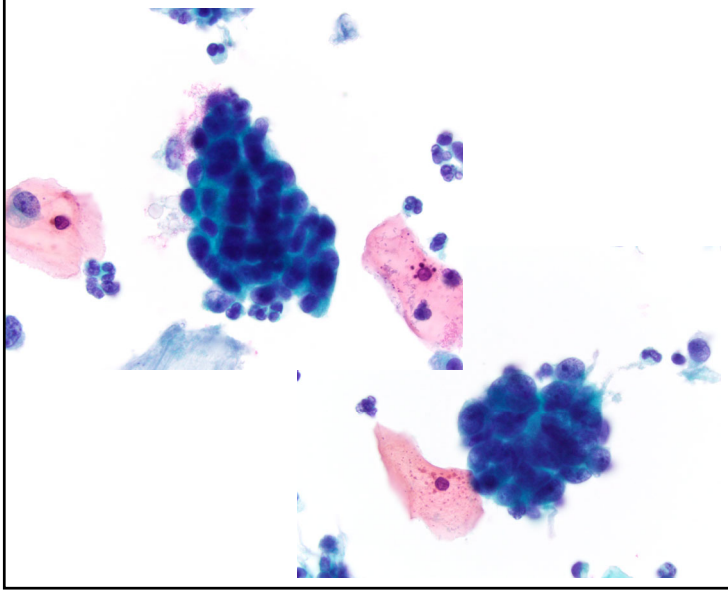
> "The performance characteristics of the immunoperoxidase, immunofluorescence, and in-situ hybridization tests have not been determined for methanol-fixed material, and therefore results need to be interpreted with caution."

Squamous Cell Carcinoma



- Poorly-differentiated squamous cell carcinoma mimics many of the features of endometrial cells:
  - Hyperchromatic groups
  - Crowding
  - High N:C ratios
  - Tumor diathesis can mimic menstrual background
- A small subset of SQC are made up of "small cells" without keratinization
- Can have mitotic activity

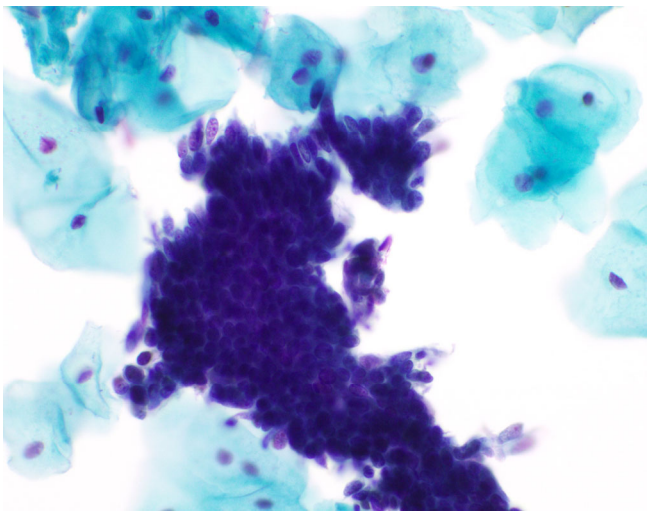
Squamous Cell Carcinoma

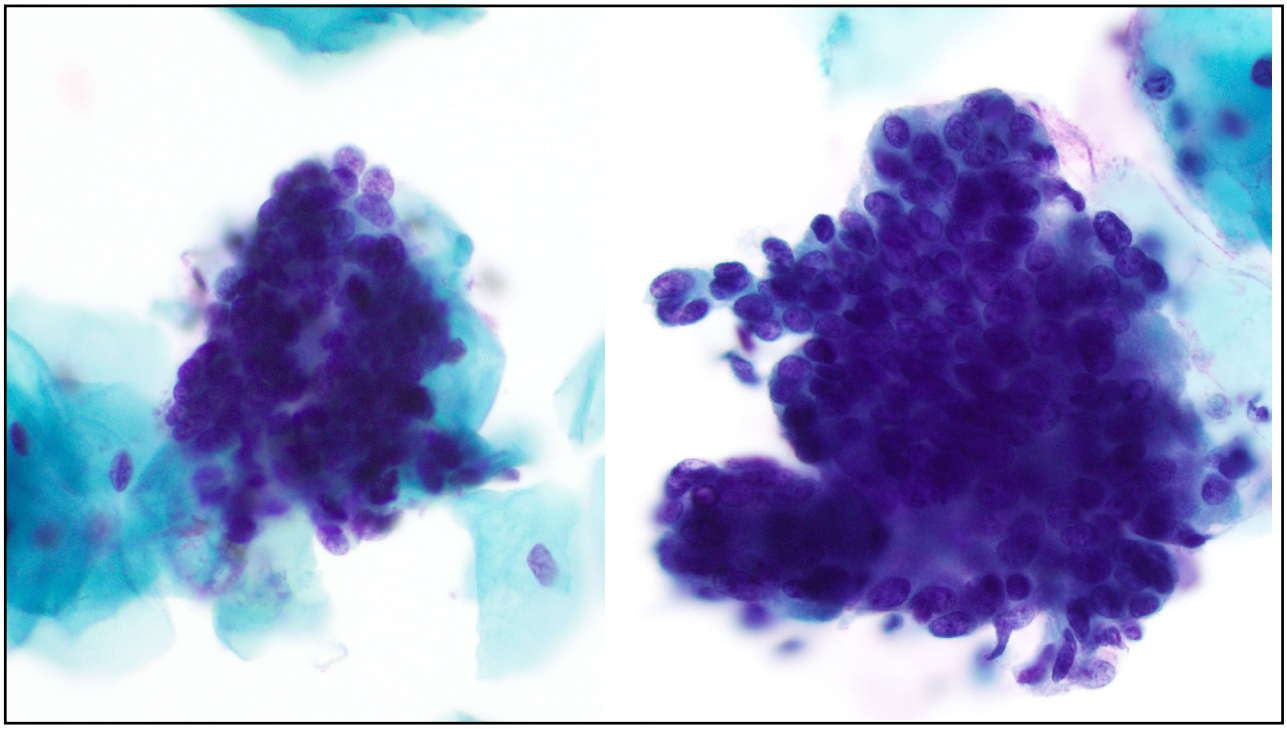


- Features favoring squamous cell carcinoma:
  - Cells typically larger than benign endometrial cells
  - Variation in cell size
  - Flat sheets
  - Single dysplastic cells - HSIL
  - Irregular nuclear contours and prominent nucleoli
  - Mitotic activity
  - HPV test results

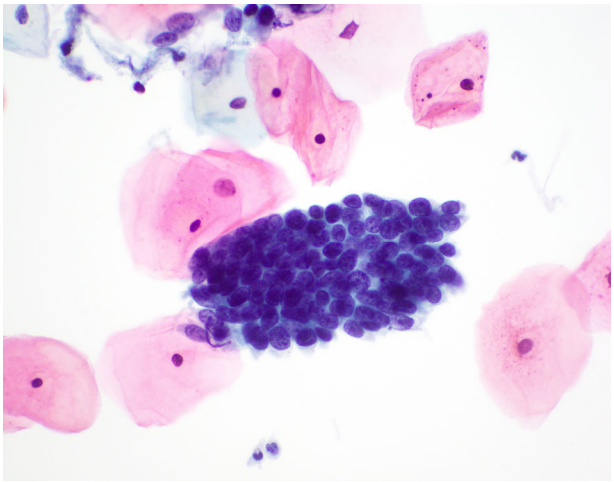
Adenocarcinoma *in situ*

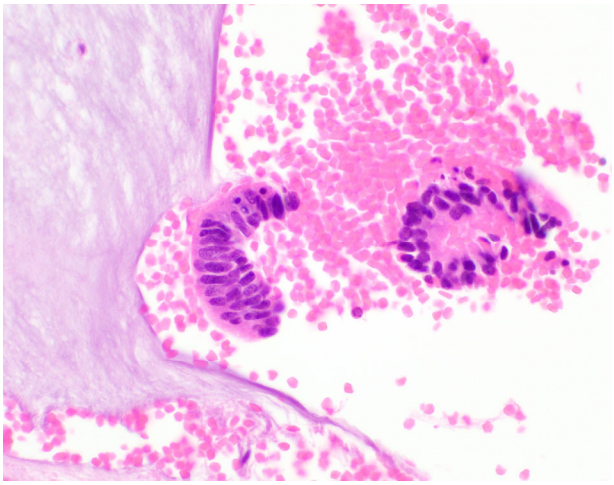
- Similarities to endometrial cells:
  - Hyperchromatic groups
  - Crowding
  - High N:C ratios
  - Can have nuclear debris
- Features favoring AIS:
  - Single cell population
  - Columnar differentiation
  - Feathering or rosettes
  - Coarse chromatin
  - Mitotic activity





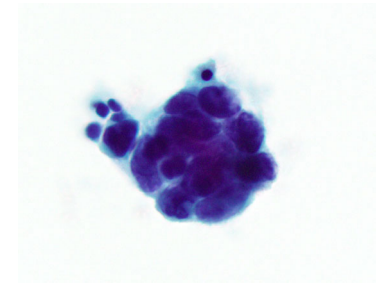
Adenocarcinoma *in situ*

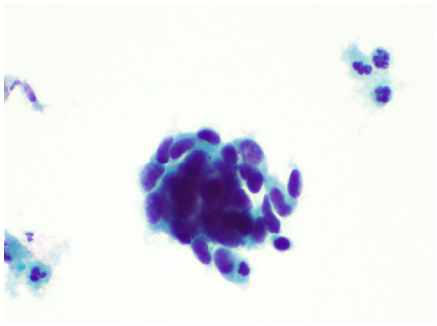


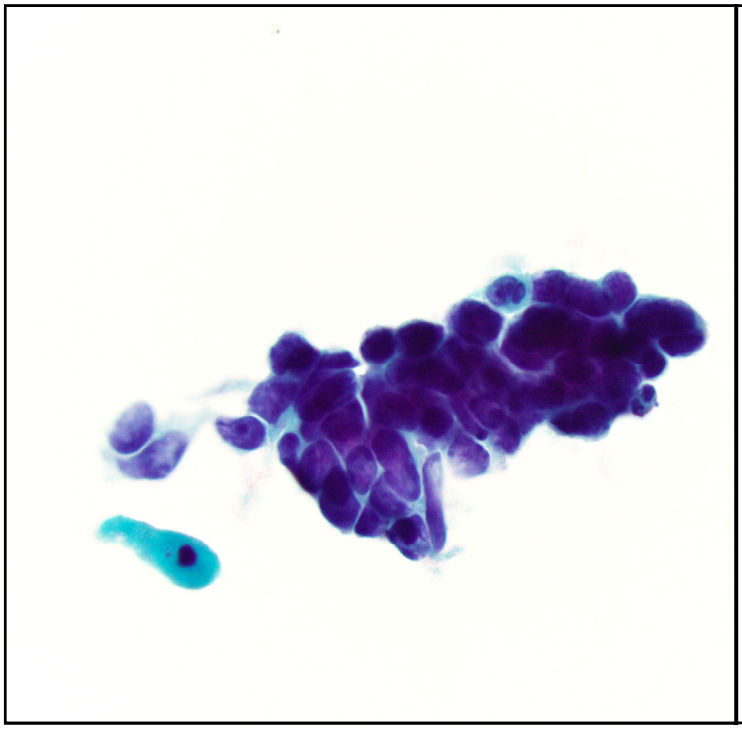


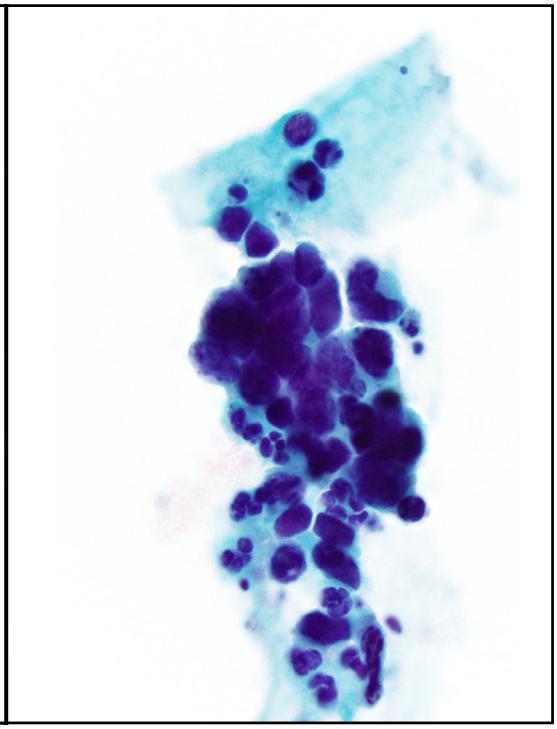
Small Cell Carcinoma

- Rare neuroendocrine carcinoma typically associated with HPV types 16/18
- Similarities to endometrial cells:
  - Clusters of highly atypical “small cells” with high N:C ratios
  - Hyperchromatic nuclei with granular chromatin that often show molding
  - Crush artifact
  - Mitotic activity









Small Cell Carcinoma

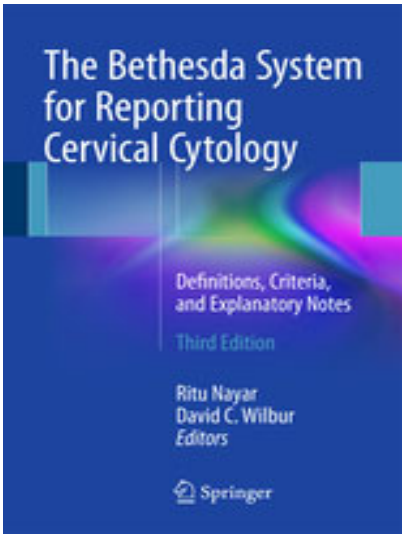
- Features favoring small cell carcinoma:
  - Cells typically larger than benign endometrial cells
  - Larger groups
  - Granular “salt and pepper” chromatin
  - More pronounced and extensive molding
  - Mitotic activity*
- Ancillary Testing
  - Cell block – expression of neuroendocrine markers
    - Up to 40% TTF-1 positive
  - HPV test results

Endometrial Cells and Their Mimics

- The distinction between benign endometrial cells and a neoplastic process is not always possible
- Features that should make you think twice:
  - Flat or irregularly contoured groups
  - Cells are columnar or have dense cytoplasm
  - Abnormal chromatin - ”salt and pepper”
  - Mitotic activity*
- Challenging cases may benefit from a cell block

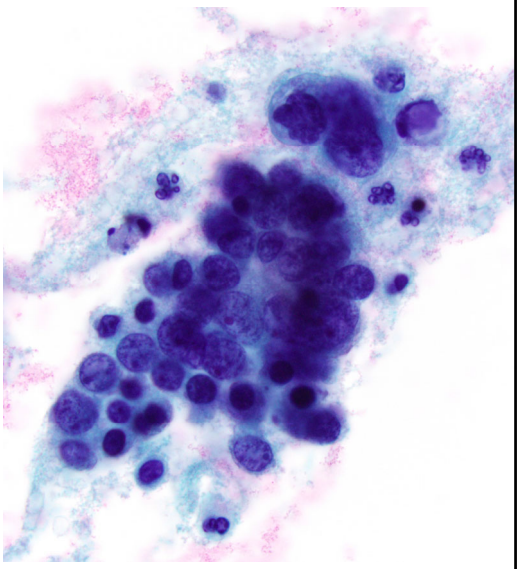
The Bethesda System

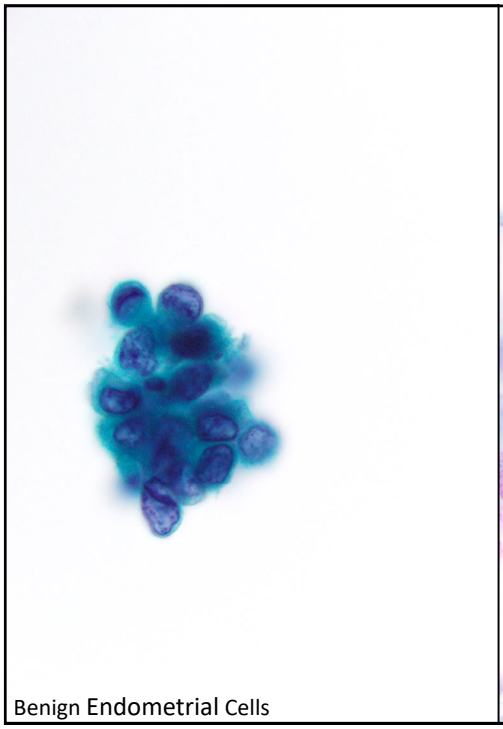
- Epithelial cell abnormality, glandular:
  - Atypical endometrial cells
  - Endometrial adenocarcinoma
- Reporting benign-appearing endometrial cells in women ≥ 45 years of age



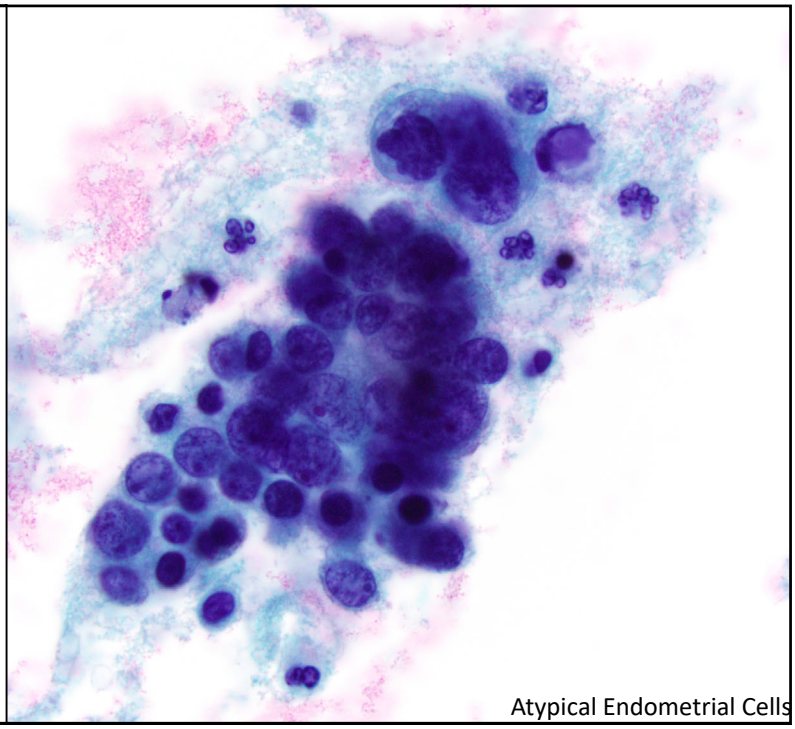
Atypical Endometrial Cells

- Isolated cells or rounded groups
- Enlarged nuclei
  - Hyperchromatic
  - Irregular contours
  - Occasional nucleoli
- Scant to moderate amounts of cytoplasm, occasionally vacuolated
- Causes:
  - Endometrial polyp, IUD, endometritis
  - Arias-Stella
  - Endometrial hyperplasia or carcinoma





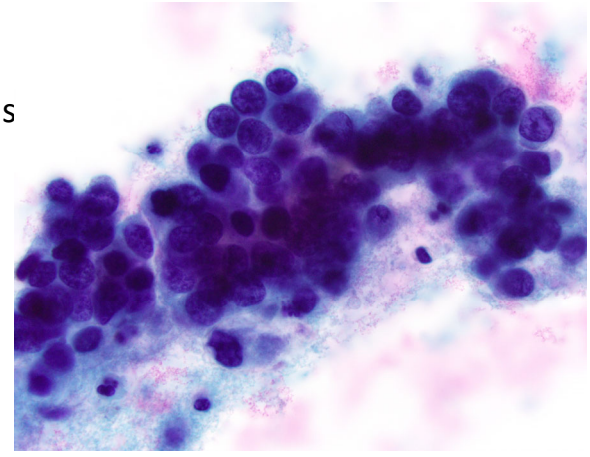
Benign Endometrial Cells



Atypical Endometrial Cells

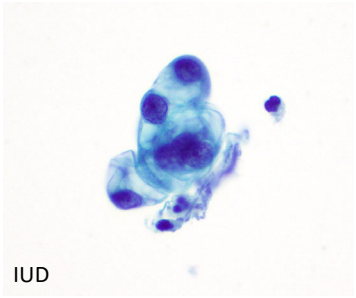
Atypical Endometrial Cells

- Reported as:
  - Epithelial Cell Abnormality – Glandular, Atypical Endometrial Cells
  - Typically not qualified as “NOS” or “favor neoplastic”

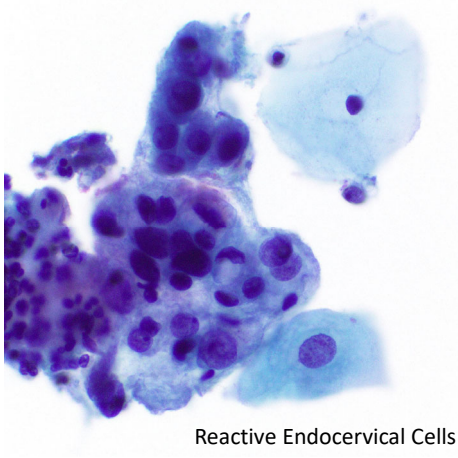


Mimics of Atypical Endometrial Cells

- Endocervical cells – reactive and atypical
- IUD
- Endocervical/endometrial polyps
- Arias-Stella



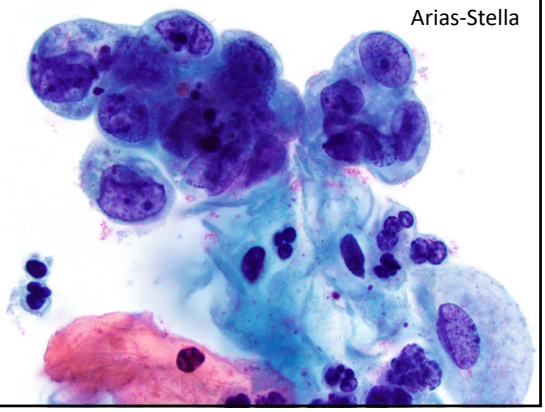
IUD



Reactive Endocervical Cells

Mimics of Atypical Endometrial Cells

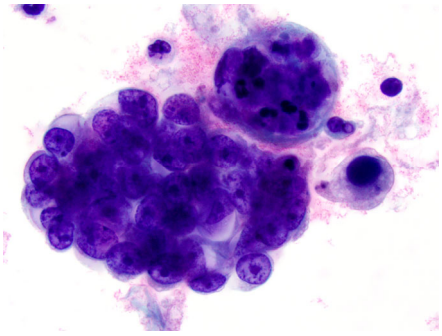
- Endocervical cells – reactive and atypical
- IUD
- Endocervical/endometrial polyps
- Arias-Stella

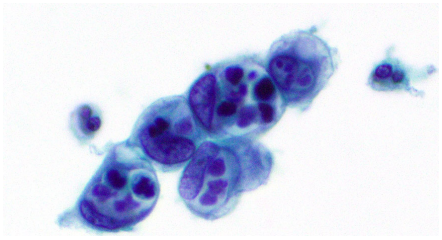


Arias-Stella

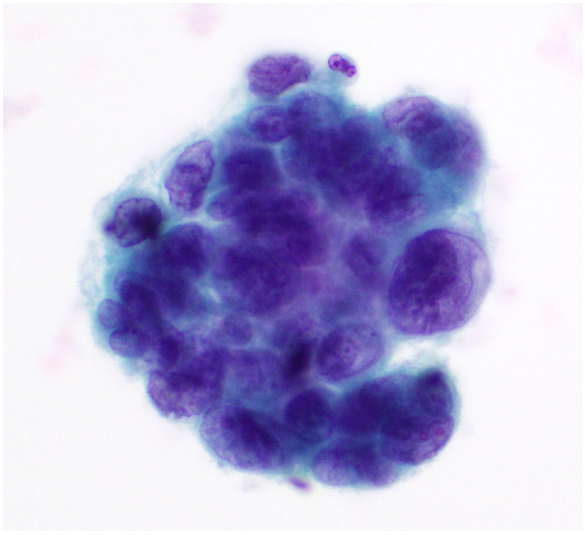
Endometrial Adenocarcinoma

- Cytologic findings determined by grade
  - Well-differentiated tumors may have only slightly enlarged nuclei compared to non-neoplastic endometrial cells
- Most commonly endometrioid
  - Isolated and small clusters of cells
  - Round cells with large hyperchromatic nuclei and prominent nucleoli
  - Variable amounts of cytoplasm, occasionally vacuolated cytoplasm
  - "Bag of polys"
  - Histiocytes in the background





High Grade Serous Carcinoma



- Pap test more likely to identify malignant cells than patients with endometrioid adenocarcinoma
- Typically large and pleomorphic cells
- Often more cellular than endometrioid carcinoma
- Psammomatous calcifications in ~25%

Differential Diagnosis – Endometrial Adenocarcinoma

- Endocervical adenocarcinoma
- Extrauterine adenocarcinoma
- Squamous cell carcinoma
- AIS
- Polyp related atypia
- Reactive endocervical cells
- IUD effect
- Arias-Stella

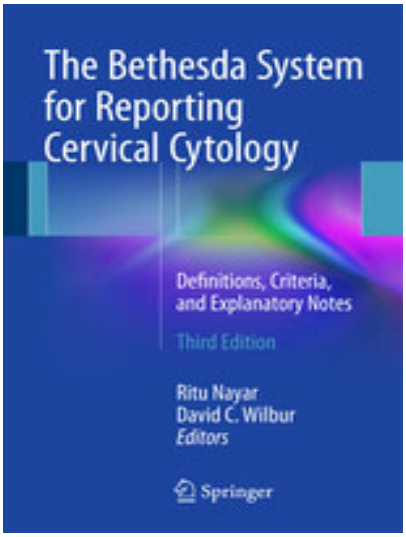
Features of AIS
Abnormal HPV test
Clinical history
Imaging studies

Reporting Benign-Appearing Endometrial Cells

- Shed endometrial cells are considered abnormal in post-menopausal women and associated with small risk of endometrial neoplasia
- First edition of the Bethesda System (1994): report benign-appearing endometrial cells in post-menopausal women
  - Status often unknown to the laboratory
- Second edition of the Bethesda System (2001): report benign-appearing endometrial cells in women $\geq$ 40 years of age
  - Selected to maximize likelihood of capturing all post-menopausal women, but lowered risk of finding endometrial neoplasia
- Post-2001 studies showed little evidence to support a role of cervical cytology identifying endometrial neoplasia in women <45 years of age

Reporting Benign-Appearing Endometrial Cells

- Third edition of the Bethesda System: report benign-appearing endometrial cells in women ≥ 45 years of age
- Diagnosis should be interpreted in clinical context
- Directly sampled lower uterine segment/endometrium should not be reported under this heading



Should the Threshold Change?

- Similar NPV for patients aged 40-44 (99.5%) and 45-49 (99.3%)

Benign-Appearing Endometrial Cells With Histopathologic Endometrial Follow-up Within 6 Months

Age, y	No. of Cases	AEH or EmCa, No. (%)	NPV, % (95% CI)
40-44	629	3 (0.5)	99.5 (98.8-99.8)
45-49	812	6 (0.7)	99.3 (98.8-99.6)
50-54	747	22 (2.9)	97.1 (96.3-97.7)
55-59	512	24 (4.7)	95.3 (94.1-96.3)
≥60	631	35 (5.6)	94.5 (92.9-95.6)
Total	3,331	90 (2.7)	97.3

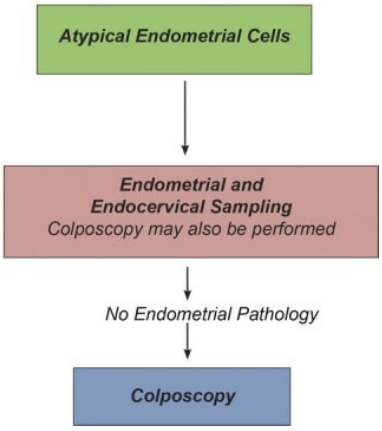
ns

p = 0.001

Yu J, et al. AJCP (2017) **148**: 274

ASCCP 2019 Management Guidelines

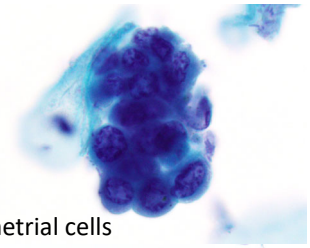
- Benign endometrial cells in patients ≥ 45 years of ages
  - Premenopausal patients: asymptomatic, no further evaluation
  - Postmenopausal: endometrial sampling
- Atypical endometrial cells: endometrial and endocervical sampling preferred (with or without colposcopy)
  - Colposcopy if no endometrial pathology identified



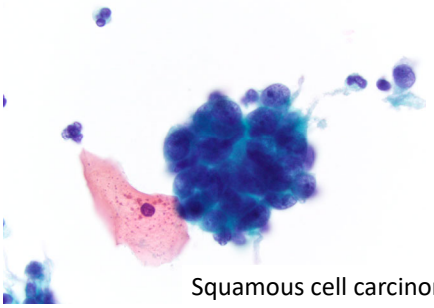
Perkins RB, et al. J. Low. Gen. Tract. Dis. (2020) **24**: 102

Conclusions

- Identifying endometrial cells – whether benign-appearing or atypical – is important to appropriately triage patients for endometrial sampling
- The distinction between benign endometrial cells and a neoplastic process is not always possible
- A cell block can be helpful in solving challenging cases
- Report benign-appearing endometrial cells in patients ≥ 45 years of age



Endometrial cells



Squamous cell carcinoma