Introduction:
A broad spectrum of benign alterations in the cytology and/or architecture of normal endometrium can be found in everyday endometrial samplings (biopsy / curettage/ polypectomy) or in endometriosis. These alterations may mimic malignancy. Furthermore, the changes may also be superimposed on an underlying malignant entity. Therefore, an understanding of these alterations and their differential diagnosis is essential to evaluation of routine endometrial samplings.

Note on Terminology: The etiology of many of these alterations is generally thought to be metaplasia, however some changes, instead, may be hormone-induced or reactive to irritants/inflammation/degeneration. This may lead to differences in terminology by various authors (i.e. “metaplasia” versus “change” versus “differentiation”). In practical terms the nomenclature is not important; instead, it is most important to be able to distinguish whether the alterations represent a benign or malignant process.

Outline of Lecture:
While these may present in combinations in the same sampling, they will be addressed in isolation for the purpose of this syllabus.

- Mucinous change
- Microglandular hyperplasia-like change
- Squamous metaplasia
- Papillary syncytial change
- Hobnail / Clear cell / Arias Stella change
- Tubal (ciliated) metaplasia
- Architectural changes following hormone treatment of atypia/cancer
- “Atypia” in endometriosis

Clinical Context: Before dismissing endometrial alterations as benign, it is important to determine whether the pathology correlates with the clinical presentation. Despite benign histology, the following clinical factors should prompt further diagnostic evaluation of the endometrium:

- Post-menopausal patient
- Thickened endometrial stripe on ultrasound
- Radiologic evidence of a uterine mass
- Prior history of atypical hyperplasia or cancer

Therefore, checking into the clinical history details or direct communication with the gynecologist is a prudent step when faced with any of these endometrial alterations. Unfortunately the reality is that many specimens are submitted with no more history than “uterine bleeding” on the specimen requisition form. The effort of a phone call is more than compensated by the increased chance to enable the correct management of a patient and avoid patient mis-management.

Ancillary Histologic “Red Flags”: Finally, before dismissing endometrial alterations as benign, two histologic features should prompt for caution:

1.) foamy histiocytes in the endometrial stroma
2.) large amounts of necrosis.

Stromal foamy histiocytes are typically seen in atypical hyperplasia or grade 1 endometrioid adenocarcinoma; thus, even small fragments of otherwise benign endometrium with foamy histiocytes in the stroma should prompt consideration of deeper level sections and/or additional sampling. Necrosis can be seen in degenerating polyps or leiomyomas, but can also be associated with malignancy. Deeper levels or additional sampling should be considered if abundant necrotic debris is present without clear cut evidence of a benign origin.
A. Mucinous Change

- Occasional intracytoplasmic mucin droplets in normal endometrium. This is within the acceptable spectrum of normal when the number of endometrial gland cells with mucin is minimal and there are no other abnormalities in cytology or architecture.

- Intracytoplasmic mucin droplets in degenerating endometrium. The endometrium associated with stromal breakdown due to anovulation or other hormonal alteration may show a spectrum of changes including cytoplasmic mucin droplets. Other changes include papillary syncytial change (see later discussion). As long as the mucin is confined to endometrium admixed with stromal breakdown, this is a benign finding.

- Mucinous epithelium with architectural complexity. In an endometrial sampling, this should not be dismissed as benign even if there is no cytologic atypia or even if the architecture falls short of criteria for endometrioid/mucinous adenocarcinoma. Unlike non-mucinous endometrioid precursors to endometrioid adenocarcinoma (i.e. complex atypical hyperplasia), cytologically bland mucinous proliferations can be found adjacent to more obvious grade 1 mucinous carcinomas or obvious grade 1 endometrioid adenocarcinomas with mucinous differentiation. In particular, the surface of these endometrial cancers may exhibit a strikingly bland mucinous appearance whereas the more obvious features of endometrioid adenocarcinoma may be restricted to the deeper portion of the tumor. Therefore if the biopsy/curettage contains only a sampling of the surface, the pathologist may mistakenly dismiss the findings as benign.

Two follow up studies of patients with endometrial samplings containing mucinous glandular proliferations demonstrated that there is a risk of finding adenocarcinoma in a subsequent hysterectomy from such patients. The risk of cancer depended on the degree of architectural complexity and ranged up to 64% to 100% in the larger study. The amount of abnormal glands in the sampling did not correlate with risk of cancer in the hysterectomy. Importantly, these architectural patterns were not necessarily accompanied by significant nuclear atypia; thus, it was the combination of mucinous change and architecture that was the key diagnostic finding. Most cancers were low grade adenocarcinomas without myometrial invasion. The most concerning architectural findings were:

- Worrisome Architectural Patterns of Mucinous Lesions That May Represent Cancer:
  - Cribriform pattern with rigid pseudolumens
  - Microglandular pattern
  - Villous / papillary pattern
  - Extensive glandular budding

Differential Diagnosis of Mucinous Change:

- Contamination by normal endocervical mucosa. Strips of normal endocervix are often incidentally admixed in endometrial samplings. Generally, endocervical epithelium has shorter nuclei than endometrial nuclei; more apically located cytoplasm which is usually lighter pink than endometrial cytoplasm; a picket-fence like orderly arrangement; and the presence of basally-located squamous metaplastic cells is a helpful diagnostic marker of endocervical derivation.

- Contamination by endocervical adenocarcinoma with intestinal differentiation. Although uncommon, some endocervical adenocarcinomas (either in situ or invasive) may exhibit mucinous/intestinal/goblet cell differentiation. Artifactual contamination of an endometrial sampling may occur. Typically, these cancers are easily recognized by the presence of nuclear atypia and mitotic activity in the mucinous epithelium.

- Metastatic mucinous adenocarcinoma. Rarely, the endometrium may be a site of spread of adenocarcinoma from other organs such as colon or stomach, which may exhibit mucinous or signet ring cell features. Finding single atypical discohesive signet ring cells, nuclear atypia, notable or atypical mitoses, cribriform architecture, dirty necrosis or segmental necrosis of mucinous epithelium should alert to the possibility of metastatic adenocarcinoma.
**Diagnostic Recommendation:** We use the term “complex mucinous endometrial proliferation” as the diagnostic line for endometrial samplings containing “mucinous epithelium with architectural complexity” that falls short of criteria for adenocarcinoma, even when no cytologic atypia is present. We add a comment explaining that while the sampling does not fulfill criteria for cancer, we cannot exclude that this is a sampling issue and that there is a possibility of unsampled cancer in the uterus, albeit likely a low grade non-invasive cancer. Since this is an unusual event, we also provide the two literature references in the comment.11, 21

**B. Microglandular Hyperplasia-Like Change**

In an endometrial sampling, the finding of what initially appears to be endocervical mucosa with microglandular hyperplasia (MGH) should be viewed with extreme caution. This is because certain endometrial adenocarcinomas and, rarely, endocervical adenocarcinomas, may demonstrate histology that mimics microglandular hyperplasia.27, 28 Such tumors, although not common, are typically mucinous adenocarcinomas or endometrioid adenocarcinomas, when viewed at hysterectomy. The MGH pattern is usually at the surface or periphery of the main tumor at hysterectomy.

- **MGH-like uterine adenocarcinoma:** Unfortunately MGH-like carcinomas may not exhibit striking nuclear atypia or mitoses, especially in the biopsy samplings. Eosinophilic change is commonly seen and may be mistaken as a benign alteration. Patient age is helpful in evaluating MGH-like changes. Most MGH-like endometrial carcinoma arises in post-menopausal women whereas most benign endocervical MGH arises in pre-menopausal women.25, 27 Exposure to exogenous hormones does not appear to be associated with this type of change in cancers so the history of hormone use is not particularly helpful in differential diagnosis. Certainly a positive history of hormone use should not be used as a criterion to dismiss MGH-like changes as benign in an endometrial sampling. A definitive diagnosis of MGH-like uterine cancer may not be possible in many cases of endometrial samplings; it is a situation parallel to that of mucinous adenocarcinoma as described above. A descriptive diagnosis and suggestion for further evaluation may be the best approach.

**Differential Diagnosis of MGH-like Carcinoma:**

- **Contamination by endocervical mucosa with MGH:** While this certainly can occur, it is probably prudent to refrain from a flat out diagnosis in an endometrial sampling unless both the clinical and pathologic findings are absolutely concordant and without any suspicious features. In particular, it would be highly unusual for this to occur in a post-menopausal woman.25 If the lesion presents in a young woman, if there are no mitoses, atypical nuclei, stromal foamy macrophages, or if the findings are obviously part of a benign polyp, then it may be reasonable to render this diagnosis, with a cautionary comment. Basally located squamous metaplastic cells also favor endocervical origin whereas apical/luminal squamous metaplasia favors endometrial origin. Conversely, it should be noted that rare examples of endocervical MGH may display mitoses, moderate nuclear atypia, or solid, sheet-like growth; so the presence of atypical findings in a sampling should not automatically be equated to malignancy.26

**Diagnostic Recommendation:** We use the term “microglandular hyperplasia-like proliferation” as the diagnostic line for endometrial samplings containing MGH-like changes that cannot be convincingly attributed to endocervical MGH (which is most of the time). The term “complex mucinous glandular proliferation” is also reasonable. In a comment we describe the problem of excluding MGH-like carcinoma, particularly if the patient is post-menopausal, and we comment on the need for clinical correlation and possible further diagnostic evaluation of the endometrium. Since this is an unusual event, we also provide the two literature references.27, 28

**C. Squamous Metaplasia**

Squamous metaplasia is commonly encountered in both benign and malignant endometrium and rarely poses a diagnostic issue. However, there are a few special settings that are worth considering because of their associated differential diagnosis. Squamous metaplasia may present as isolated stratified mounds within endometrial glands (non-morular growth) or may present as morules (solid, circumscribed round nests of
concentrically arranged squamous appearing cells. In addition, a discussion of peritoneal keratin granulomas makes sense here, though this entity is not exactly squamous metaplasia per se.

- **Non-morular squamous metaplasia:** This type of change can be isolated, focal or scattered in an endometrial sampling and has been proposed to be a reactive change in the setting of irritation (e.g. intrauterine device), trauma or infection. When present to a limited degree and without cytologic atypia, it is of no clinical significance.

**Differential Diagnosis of Non-Morular Squamous Metaplasia:**

- **Placental site nodule:** The epithelioid appearance of trophoblast cells in a placental site nodule (PSN) can mimic squamous metaplasia of the endometrium. PSN is usually found in young women, though some cases have been identified 8 years following antecedent pregnancy. Still it would be unusual to find a PSN in a post-menopausal woman. Typically the trophoblast are embedded in a hyalinized eosinophilic background, which helps to make the diagnosis. For diagnostic confirmation, immunostaining for keratin is not helpful since trophoblast will mark with keratin; therefore, inhibin or hPL are the key immunostains.

- **Endometrial extension of cervical squamous dysplasia:** Though uncommon, squamous dysplasia may extend from the upper endocervix into the uterine cavity by replacing with mucosa of the lower uterine segment and even endometrial cavity. Generally the diagnosis should be evident by nuclear atypia and mitoses. Positive immunostaining for p16 and MIB-1 can be of value when trying to determine whether dysplasia has grown into the endometrial lining since neither marker should be expressed in squamous metaplasia of the endometrium.

- **Endometrial involvement by cervical squamous cell carcinoma:** As in the case of cervical squamous dysplasia, the nuclear features should be evident. Irregular contours of cell aggregates, premature cytologic differentiation, and necrosis should also raise concern for carcinoma. As in the case of cervical squamous dysplasia, evaluation of the cervix and use of immunostaining for p16 and MIB-1 may be helpful.

- **Endometrial squamous cell carcinoma:** This is a rare entity and should be a diagnosis reserved for hysterectomy specimens in which the possibility of a primary cervical cancer with endometrial extension can be definitively excluded since the two may resemble each other in an endometrial sampling.

- **Ichthyosis uteri:** Another rare entity that appears to be declining in incidence, ichthyosis uteri is a benign process in which the endometrial lining has been replaced by a cytologically benign stratified proliferation of cells with squamous differentiation. It has been associated with chronic endometritis and with heat ablation of the endometrium. In comparison to garden variety non-morular squamous metaplasia of the endometrium, a sampling of ichthyosis uteri (besides being much less common) would likely contain a much greater abundance of tissue involved by squamous features.

- **Morular squamous metaplasia:** This refers to well-defined, circumscribed solid round nests of squamous appearing cells that fill and expand endometrial glands. The cytology is entirely bland (no atypia or significant mitoses) in the squamous appearing cells. Central necrosis within the morules can be present but has no bearing on whether the process is benign or malignant. It is the glandular component involved by and adjacent to the morules that defines how the sampling should be classified. Morules typically arise within hyperplastic endometrium (usually which is atypical) or well-differentiated endometrioid adenocarcinoma. It is not common to see them in higher grade tumors. A recent study demonstrated that cancer developed in 2/40 (5%) cases of morules in non-atypical endometrium versus in 5/26 (19%) cases with atypical endometrium. Thus, diagnostic attention should be directed to the glandular epithelium.

The etiology of morular metaplasia is not fully understood but they appear to develop along a pathway that is different than that of the adjacent glands since they tend to be found only in low-grade lesions; they lack immunoeexpression of estrogen and progesterone receptors, and they persist following progestin medical therapy despite response of the glandular component.
Differential Diagnosis of Morular Squamous Metaplasia:

- All of the entities in the differential diagnosis of non-morular squamous metaplasia: See discussion above.

- Atypical polypoid adenomyoma (APA): This is a clinically distinct entity arising as a polypoid lesion in women in their 30's and 40's. Histologically it is composed of an endometrial glandular proliferation embedded in a myomatous or myofibromatous stroma; endometrial stromal is lacking. Some degree of atypical hyperplasia is generally present. APA enters the differential diagnosis in endometrial samplings because it often exhibits striking morular metaplasia with central necrosis. Distinction from adenocarcinoma or complex atypical hyperplasia is made by recognition of the distinct myomatous stroma, the patient age, and the clinical presentation as a polypoid uterine lesion.

- Epithelioid uterine smooth muscle tumor: Extensive morules in a fragmented sampling may mimic these rare entities, which are worth entertaining in the differential diagnosis if no glandular epithelium is present in the sampling. Some examples may show polygonal cell shape and eosinophilic cytoplasm mimicking squamous cells. The transition of the morular epithelium from adjacent glandular epithelium would exclude this diagnostic consideration.

- Epithelioid trophoblastic tumor: This is also exceedingly rare but worth considering in a young woman if no glandular epithelium is present in the sampling along with the morular epithelium. Polygonal cell shape and eosinophilic cytoplasm may resemble squamous cells but these tumors show nuclear atypia, mitoses and necrosis.

Diagnostic Recommendation: We classify samplings with morular metaplasia using the same criteria and terminology used for non-morular findings: i.e Complex atypical hyperplasia with squamous (morular) differentiation; adenocarcinoma with squamous (morular) differentiation. Morules should not count as solid growth in the grading of endometrioid adenocarcinoma. Occasionally morules may be found in non-atypical hyperplasia. These generally have a benign outcome. Rarely, samplings may contain isolated morules without adjacent glands. In these settings it is worth mentioning consideration of re-sampling (to guard against the possibility of un-sampled atypical endometrium) and close follow up given the risk, albeit minor, of developing cancer.

- Peritoneal keratin granulomas: Though technically not squamous metaplasia of the peritoneum, per se, this entity fits in the discussion of squamous metaplasia in endometrioid lesions. This refers to the finding of nests of keratinized squamous epithelium surrounded by foreign-body type giant cells (multinucleate histiocytes) either on the peritoneal surface or within subperitoneal connective tissue. These so-called keratin granulomas do not contain any glandular epithelium. They are found in patients who have a prior or current endometrioid adenocarcinoma with squamous differentiation of the uterus, ovary or fallopian tubes; atypical polypoid adenomyoma has also been reported to be associated with this finding. It is proposed that these occur via transtubal spread of the squamous metaplastic cells to the peritoneum, resulting in a foreign body type reaction and so-called keratin granuloma formation. These may be visible to the surgeon and mimic peritoneal carcinomatosis. As long as no glandular component is identified, keratin granulomas should not be considered tumor spread and should not result in upstaging.

Differential Diagnosis of Peritoneal Keratin Granulomas:

Finding peritoneal keratin granulomas in a patient who has no history of cancer can be explained by a few non-neoplastic scenarios, described below. However, if there is no evidence to support of any of those diagnostic scenarios, clinical/radiologic evaluation of the uterus/ovaries for adenocarcinoma with squamous differentiation should be considered.

- Ruptured ovarian teratoma: Cystic ovarian teratomas may occasionally rupture in situ. If keratinizing squamous teratomatous elements spill into the peritoneal cavity, the keratin may elicit a peritoneal foreign body giant cell reaction that may clinically resemble peritoneal carcinomatosis. History of an ovarian cyst or ovarian teratoma would be the key diagnostic clue.
- **Spilled amniotic fluid (vernix caseosa peritonitis):** Emergency Cesarean-section delivery can sometimes be accompanied by spillage of amniotic fluid into the peritoneum during the procedure. If the clinical setting does not allow for copious irrigation of the pelvic cavity (i.e. traumatic or emergent operation), fetal squamous cells floating in the amniotic fluid can elicit a peritoneal foreign body giant cell reaction that may clinically resemble peritoneal carcinomatosis. We have encountered cases in which a young woman presents for tubal ligation subsequent to a C-section and the surgeon encounters what appears to be diffuse peritoneal studding. Biopsies of the peritoneal nodules will contain granulomatous inflammation and keratinized squamous cells; acute and/or chronic inflammation may also be present. Fragments of hair shafts are a further diagnostic clue to the origin from either amnion or a teratoma. This entity is also referred to as vernix caseosa peritonitis.6, 18, 19

- **Intraperitoneal renal dialysis-associated peritoneal squamous metaplasia:** This has been reported in a few patients and may result in a diffuse or multi-micro-nodular distribution, sometimes mimicking peritoneal carcinomatosis.7

D. **Papillary Syncytial Change**

Papillary syncytial change is most often seen in samples with glandular and stromal breakdown. This refers to the changes in the surface epithelium associated with condensed endometrial stromal cells, often forming so-called endometrial stromal “blue balls”. Instead of columnar cell shape, polarized nuclei (located at the cell base), and well-defined cell membranes, the endometrial glandular epithelium overlying the degenerating stroma shows polygonal cell shape, loss of polarity (piling up), and syncytial appearance. Varying degrees of budding, piling up, stratification, and micropapillary tufting can occur. No atypical nuclear changes, atypical mitoses, or increase in nuclear/cytoplasmic ratio occurs. In fact, these cells often acquire more pink cytoplasm than normal endometrial epithelium.

**Differential Diagnosis of Papillary Syncytial Change:**

- **Uterine serous carcinoma:** Extensive papillary syncytial change can resemble uterine serous carcinoma at low magnification due to the papillary architecture. The distinction between the two relies on evaluating the nuclei and the nuclear/cytoplasmic ratio. Serous carcinoma typically has a high N/C ratio, whereas a low N/C ratio is expected in papillary syncytial change due to acquired cytoplasm. Serous carcinoma should exhibit nuclear enlargement, hyperchromasia, irregular nuclear contours, macronucleoli, brisk and/or atypical mitoses, and strong diffuse p53 and p16 immunoperoxidase. None of these should be found in papillary syncytial change. The presence of true condensed endometrial stroma also favors a benign diagnosis.

- **Papillary variant endometrioid adenocarcinoma:** Occasionally, papillary architecture can be seen in endometrioid adenocarcinoma in one of two major patterns: villoglandular growth or small non-villous papillary growth.3 The latter may closely resemble papillary syncytial change. The key clue to the latter is the absence of any glandular or solid growth pattern of endometrioid adenocarcinoma. It would be unlikely for an endometrial sampling of papillary endometrioid adenocarcinoma to contain only the small non-villous papillae and not any component of glandular/solid tumor. The presence of true condensed endometrial stroma also favors a benign diagnosis.

**Diagnostic Recommendation:** Unless there is exuberant papillary syncytial change, we generally do not comment in the report on its presence. If there is a notable degree present, we may consider a short comment explaining how we excluded a diagnosis of malignancy.

E. **Arias Stella Reaction**

This is a well-recognized alteration seen in gestational endometrium, consisting of clear cell change, cytomegaly, nucleomegaly, smudged and/or vacuolated chromatin, exaggerated papillary tufting, and/or hobnail growth. The diagnosis is typically straightforward, particularly since the sampling will often contain
other gestational features such as decidua, placental and fetal tissue. However, Arias Stella reaction can be present in the endometrium following a spontaneous abortion; in such cases, the patient may not even know she was pregnant and an endometrial sampling performed after a time of bleeding may only contain a bit of residual involuting endometrium that does not contain features of well-developed decidualization. In the absence of a good clinical history and in the absence of good decidualization, the presence of Arias Stella reaction in involuting endometrial glands may be mistaken for clear cell carcinoma.

**Differential Diagnosis of Arias Stella Reaction:**

- **Clear cell carcinoma:** The combination of clear cytoplasm and hobnail growth in Arias Stella Reaction can mimic tubulocystic/tubuloglandular variant clear cell carcinoma at first glance. However, clear cell carcinoma should exhibit mitotic activity, nucleoli and a greater degree of nuclear atypia. The clinical context is important since clear cell carcinoma would be uncommon in a recently pregnant young woman. As mentioned above, however, patients may not always know they were pregnant if a spontaneous abortion occurs in early trimester. The presence of other growth patterns such as papillary and solid clear cell carcinoma are also helpful clues. Diffuse strong HNF-1 nuclear immunoexpression can also be used to support a diagnosis of clear cell carcinoma.

**F. Hobnail Change**

This is an uncommon alteration in the endometrium and, when it does occur, most often occurs within polyps in our experience. The glandular epithelium takes on a hobnail appearance in which the cells show a bulbous apical shape with an apically located nucleus that may be increased in size. Some cases also show a limited degree of piling up or papillary tufting. No nuclear atypia or abnormal mitoses should be present. The main differential diagnosis is with clear cell or serous carcinoma.

**Differential Diagnosis of Hobnail Change:**

- **Clear cell carcinoma:** Nuclear atypia (enlargement, hyperchromasia, irregular contours), increased and/or atypical mitoses, nucleoli and strong diffuse nuclear HNF-1 immunoexpression should raise consideration of clear cell carcinoma; these features are not expected in hobnail change.

**Diagnostic Recommendation:** Even when there are no features suspicious of malignancy, it is probably best to advise at least close follow up, given the rarity of this finding relative to clear cell or serous carcinoma.

**G. Atypical Findings in Endometriosis**

Both the glands and stroma forming endometriosis may undergo a spectrum of alterations and neoplasia that are similar to those of the uterine endometrium. At the malignant end of the spectrum, patients may develop adenocarcinoma (typically endometrioid adenocarcinoma or clear cell carcinoma), adenosarcoma, or even endometrial stromal sarcoma from within the focus of endometriosis. At the other end of the spectrum, reactive nuclear changes may be seen, as well as many forms of metaplasia including tubal, eosinophilic and mucinous metaplasia. In our experience, the most problematic finding in endometriosis is nuclear atypia.

- **Nuclear atypia in endometriosis** Occasionally reactive changes may be noted in the endometrial glandular epithelium, consisting of nuclear enlargement, hyperchromasia and tiny nucleoli; variable degrees of nucleocytomegaly can occur. These alterations are usually focal within a specimen, involving small patchy areas of endometriosis. Importantly, the chromatin has a smudged or degenerative appearance rather than the coarse texture seen in serous or clear cell carcinoma. This has been reported in up to 22% of cases, when adequate sampling and attention is directed to the endometrial epithelium. The clinical significance of nuclear atypia depends on whether or not hyperplastic changes are present. In the absence of hyperplasia, nuclear atypia has no clinical significance. If there is underlying endometrial hyperplasia within the endometriosis, then a diagnosis of atypical hyperplasia should be considered.

- **Mucinous metaplasia in endometriosis** Mucinous metaplasia can be seen in some cases of endometriosis. In the absence of nuclear atypia or significant hyperplasia, this is not clinically significant. Rarely, mucinous
tumors may arise in ovarian endometriosis, such as mucinous borderline tumors, and mucinous metaplasia may represent the precursor change.

**Diagnostic Recommendation:** When either nuclear atypia or mucinous metaplasia is identified in ovarian endometriosis (or peritoneal endometriosis), it is a good idea to consider the adequacy of specimen sampling. In large ovarian endometriosis specimens which have undergone representative sampling, it may be worth submitting more tissue from the most solid components to exclude the possibility of a worse lesion. In general, care should be taken in sampling larger specimens of endometriosis since foci of endometrioid adenocarcinoma or clear cell carcinoma may be small and may not have any grossly identifiable features distinguishing it from the remainder of the specimen or from the blood clot. Because cancer foci may resemble blood clot within endometriosis, its a good idea to avoid rinsing away bloody cyst contents under a faucet. Instead, the bloody cyst contents can be gently evacuated by submerging the specimen in a container of formalin and gently shaking the specimen. Remaining “blood clots” should be carefully examined to exclude the possibility that they represent cancer.

**H. Hormone Treatment of Atypical Hyperplasia / Low-grade Adenocarcinoma**

Non-surgical treatment of atypical hyperplasia or grade 1 endometrioid adenocarcinoma is an acceptable first line option in some pre-menopausal women seeking fertility-preservation or in some women who are poor surgical candidates. This approach is not offered for higher grade endometrioid adenocarcinoma or tumors of other histologic subtype. Non-surgical treatment consists of either oral progestin therapy or progesterone-releasing intrauterine device. Though several months of therapy are often required, it has been reported that around 60% to 70% of such women can achieve a successful result without need for surgery. This therapy, however, requires careful surveillance, including interval endometrial sampling surveillance, to ensure response to treatment. Thus, pathologists play an important role in guiding therapy by their evaluation of these interval surveillance samplings. The clinician’s primary question to the pathologist is whether the tumor is responding (and if so, to what degree); if it is not responding, is the tumor progressing from atypical hyperplasia to adenocarcinoma or from low grade adenocarcinoma to higher grade?

The diagnostic challenge posed by progestin-treated surveillance samplings are several-fold:

1. Progestin may cause cytologic atypia to be suppressed, leading to potential underdiagnosis of residual disease.
2. Progestin may cause architectural changes that do not fulfill conventional criteria for carcinoma, leading to potential underdiagnosis of residual disease.
3. Progestin may cause a host of metaplastic alterations that may lead to overdiagnosis of residual disease.
4. Lack of access to clinical history of atypia/cancer may lead to underdiagnosis of residual disease.
5. Progestin may not always result in stromal decidualization, leading to underdiagnosis of residual disease if no clinical history is provided.
6. There is no consensus on the terminology to be used in evaluating progestin-treated lesions; very few clinico-pathologic outcome studies exist.

In summary, the findings of residual disease may not be easily recognized in a patient on progestin therapy because the diagnostic criteria are different in this setting than in a non-treated patient.

One of the more recent, large, detailed clinical-pathologic outcome studies suggested that the key elements that predict response to progestin therapy are the duration of treatment and the presence of abnormal architecture and/or nuclear atypia. The definitions used in this study are important to highlight: Abnormal architecture refers to the presence of any of the following: crowded glands, cribriform fused glands, papillary branching glands or any pattern fulfilling conventional criteria for adenocarcinoma. Nuclear atypia refers to any of the following: coarse chromatin or nucleoli. The presence of either abnormal architecture or nuclear atypia was defined as “residual disease”. In this study, any residual disease found in a surveillance sampling
at 7-9 months was an adverse finding predicting failure of medical treatment. However, there was no outcome significance of residual disease at earlier time points in surveillance; up to about 40% of patients with residual disease at 4-6 months of treatment still achieved complete resolution or regression of disease.

Clinician GYN practice patterns in this setting vary across institutions. In our institution (personal communication from Dr Lee-may Chen, UCSF Gynecologic Oncology, April 2010), the general approach is that an appropriate candidate for hormonal treatment can be offered treatment for about 6-9 months with interval endometrial samplings every 3 months. If the interval samplings show a quantitative and qualitative decrease in residual disease, treatment is continued until the 9 month surveillance sampling; if no residual disease is present, the treatment is successful; otherwise, hysterectomy is offered. If any surveillance sampling ever shows an increase in the quantity or complexity of residual disease, or shows progression of pre-treatment atypical hyperplasia to clear cut cancer, or progression of pre-treatment low grade cancer to higher grade cancer, then hysterectomy is considered.

**Diagnostic Recommendation:** In general, it is best to retrieve all the prior endometrial samplings (or at least the most recent one) for direct comparison to the current sampling.

**If the residual abnormal findings clearly fulfill the conventional WHO criteria of atypical hyperplasia or adenocarcinoma:**

1. We use the diagnostic terminology “Residual progestin-treated atypical hyperplasia” or “Residual progestin-treated endometrioid adenocarcinoma”.
2. We comment on whether normal endometrium is present and whether progestin-induced changes are present (stromal decidualization, reduction in gland number/size).
3. We review the pre-treatment biopsy and any interval samples and report whether the quantity of residual disease is approximately the same, less or more compared to the most recent sampling.

**If the residual abnormal findings do not clearly fulfill the conventional WHO criteria of atypical hyperplasia or adenocarcinoma, we look for any one of these findings as evidence of residual disease:**

- Crowded glands
- Papillary branching glands
- Fused glands
- Cribriform glands
- Nucleoli
- Coarse chromatin

1. We use the diagnostic terminology “Residual progestin-treated atypical glandular proliferation” and comment that this likely represents partially suppressed / partially treated atypical hyperplasia or carcinoma (depending on what the original diagnosis was).
2. We comment on whether normal endometrium is present and whether progestin-induced changes are present (stromal decidualization, reduction in gland number/size).
3. We review the pre-treatment biopsy and any interval samples and report whether the quantity of residual disease is approximately the same, less or more compared to the most recent sampling.

**If there is no residual abnormality (i.e. none of the criteria listed above):**

1. We use the diagnostic terminology “No residual glandular abnormalities”
2. We comment on whether normal endometrium is present and whether progestin-induced changes are present (stromal decidualization, reduction in gland number/size).
3. We comment on reviewing the most recent interval sampling.


