Abnormal uterine bleeding (AUB) is a common sign of a number of different uterine disorders ranging from dysfunctional (nonorganic) abnormalities or complications of pregnancy to organic lesions such as polyps, hyperplasia, or carcinoma. In many cases, AUB leads to endometrial biopsy or curettage that can present unique diagnostic challenges for pathologists. There are a variety of terms are applied to AUB. Dysfunctional uterine bleeding (DUB) refers to bleeding due to ovulatory dysfunction with no other uterine or systemic abnormality present. Post-menopausal bleeding (PMB) describes uterine bleeding one year after the cessation of menses. By definition, DUB excludes postmenopausal bleeding or bleeding due to the presence of specific pathologic processes such as inflammation, polyps, hyperplasia, carcinoma, exogenous hormone effects, and complications of pregnancy. The endometrial changes associated with DUB are important to recognize, because they may be confused with more serious lesions such as hyperplasia.

A frequent concern, especially in the perimenopausal and postmenopausal patient, is the presence of hyperplasia or carcinoma of the endometrium. Overt hyperplasia or neoplasia often is the least troublesome problem from a diagnostic point of view. A variety of other, benign patterns are more commonly seen and present some of the greatest challenges in biopsy interpretation since they are difficult to catalog. Artifacts, superimposed patterns of breakdown and bleeding, ovulatory disorders, hormonal effects, and metaplasia all contribute to the complexities of interpreting these cases.
DYSFUNCTIONAL UTERINE BLEEDING

Dysfunctional uterine bleeding is a clinical term that refers to bleeding due to irregularities in ovarian function, so it is most common at the time of menopause. DUB is largely a diagnosis of exclusion once other etiologies such as organic lesions, endometritis and systemic bleeding disorders are ruled out. Endometrial biopsy or curettage is usually done to determine if endometrial changes are consistent with DUB and to exclude other causes of bleeding, especially organic lesions in the perimenopausal woman. These biopsies are common in many practices, usually showing benign changes that may be complicated by breakdown and bleeding and by abnormal endometrial development that is neither hyperplastic nor neoplastic.

DUB-associated patterns have the stigma of lacking glamour of a more rare and significant diagnosis such as atypical hyperplasia. Despite their somewhat banal nature, they can be complicated to interpret and may require considerable study. The terminology applied to the consequences of dysfunctional patterns also has not been the target of strict conventions of nomenclature, probably allowing many different terms for groups of fundamentally similar changes.

DUB can be due to anovulatory cycles or to disorders in follicle development during the luteal phase. In most cases, DUB is due to anovulatory cycles, and some authors regard anovulation as the only cause. Alternatively, however, a shortened or prolonged luteal phase may also lead to abnormal bleeding, concepts known as “luteal phase defect” and “irregular shedding.”

Anovulatory bleeding pattern (proliferative with glandular and stromal breakdown). Most cases of DUB are due to anovulatory cycles, a sporadic but common occurrence, especially in perimenarchal and perimenopausal women. Anovulatory cycles are also a component of polycystic ovarian disease or Stein-Leventhal syndrome with more persistent endocrine imbalance in the reproductive years.

In the normal menstrual cycle a cohort of follicles is recruited and they begin to develop and produce estradiol. A dominant follicle then ruptures following the LH surge at mid-cycle. After the follicle ruptures, a corpus luteum develops, producing progesterone as well as estradiol.
In anovulatory cycles the follicles are recruited but there is no ovulation, usually due to disorders at the hypothalamus/pituitary level or feedback signals. As a consequence, there is a surge of estradiol without progesterone from a corpus luteum. The follicle or follicles can either involute leading to estrogen withdrawal or persist leading to sustained estrogen stimulation of the endometrium. In either event the endometrium proliferates without a normal luteal phase. With estrogen withdrawal, breakdown occurs in a weakly proliferative background as the estrogen stimulus wanes (estrogen withdrawal bleeding). With estrogen persistence, the endometrium continues to proliferate with thrombi forming in superficial vessels leading to areas of breakdown (estrogen breakthrough bleeding). In either case the breakdown often affects only a portion of the endometrium.

The usual morphologic reflection of anovulatory cycles is a proliferative phase pattern, often with fibrin thrombi in small vessels and breakdown and bleeding superimposed. If active bleeding is not taking place at the time of biopsy, then the changes are simply those of proliferative phase patterns. These common histologic findings are important to observe since they provide useful information for the gynecologist. Tissue fragmentation and artifacts along with the breakdown patterns often distort the tissue, but the anovulatory bleeding pattern usually is recognizable.

**Disordered proliferative phase.** The disordered proliferative phase pattern usually is an extension of anovulatory cycles due to persistent estrogen stimulation. In this situation the endometrium is proliferative but shows focal gland irregularities including dilatation and branching like that seen in hyperplasia. In contrast to hyperplasia, however, gland irregularities are mild and focal in the disordered proliferative phase pattern.

The diagnosis of disordered proliferative phase pattern has become commonplace in many practices. This term is often overused and misapplied, however. Changes such as fragmentation, telescoping and even portions of basalis can be misclassified as disordered proliferative phase patterns. In addition, the distinction between disordered proliferative patterns and simple hyperplasia is blurred in some situations. To be clinically useful this diagnosis should be reserved for those cases that truly show focal irregularities in proliferative gland
development. Besides anovulatory cycles, limited sampling of a polyp may yield a pattern of disordered glands.

**DUB and secretory changes.** DUB may also develop when ovulation occurs but the corpus luteum does not develop and persist for a normal duration over the last half of the menstrual cycle. Disturbances in the rate and amount of progesterone produced by the granulosa cells of the corpus luteum result in alterations in the pattern of secretory phase development. These changes may be due to insufficient development or persistence of the corpus luteum (luteal phase defect, LPD) or to abnormal persistence of a corpus luteum (irregular shedding). (13-16)

Luteal phase defect and irregular shedding are less well-defined entities. These conditions, if they occur, are sporadic and not amenable to detailed clinical-pathologic correlations to clearly define the morphologic changes. There are no well-defined morphologic changes that are diagnostic of disturbed corpus luteum function. There are clear situations, however, where there is abnormal secretory phase maturation with or without superimposed non-menstrual breakdown.

The term “irregular maturation” describes secretory endometrium that does not show a normal and universal pattern of secretory development that allows clear histologic dating according to established criteria. The endometrium can show marked variation in secretory development from area to area with some glands demonstrating tortuosity and secretions while other glands are underdeveloped, lacking these changes. It is not clear that these patterns truly reflect an inadequate corpus luteum, but the descriptive diagnosis serves to indicate that abnormal but benign secretory changes are present and clinical correlation is needed. When bleeding is present in a secretory but non-menstrual background, a descriptive diagnosis of “secretory bleeding pattern” with a brief comment serves to communicate the changes to the clinician. Rarely irregular shedding may result in a mixed phase pattern due to abnormal persistence of the corpus luteum. In this case portions of the endometrium are secretory and others areas have proliferative features.

Recognition of abnormal secretory phase patterns is important. The best method to detect these changes is to recognize when secretory endometrium does not show a consistent pattern of
normal “datable” changes. Usually, it is not possible to determine the etiology, and there are a number of possible causes of abnormal secretory changes in addition to ovulatory dysfunction (Table 1). Consequently, a descriptive diagnosis without assigning an underlying cause is the best approach for the pathologist.

**BREAKDOWN PATTERNS AND METAPLASIA**

**Glandular and stromal breakdown.** When endometrium undergoes acute non-physiologic (non-menstrual) breakdown and bleeding, glandular and stromal changes occur that are almost unique to this tissue.(1) Fibrin thrombi form in small arteries and capillaries or in dilated superficial venules resulting in apoptosis with nuclear debris at the base of glands and within the stroma.(17-19) The devitalized tissue then demonstrates a characteristic pattern of collapse as the stromal cells condense into tight clusters with scant cytoplasm and hyperchromatic, closely apposed nuclei. As these clusters of stroma ("blue balls") separate from underlying intact endometrium, they often retain a cap of epithelial cells, resulting in small round to polypoid tissue fragments. The breakdown pattern is highly variable, ranging from limited foci to diffuse changes with extensive fragmentation of the tissue. As bleeding continues and becomes chronic the endometrium may show other features including hemosiderin deposition, foam cells, and stromal hyalinization (Table 2).

Another change that reflects breakdown and bleeding is eosinophilic syncytial change (ESC).(20-22) This alteration, also termed “papillary syncytial change,” occurs along the surface epithelium, occasionally extending superficially into glands. Other features of active bleeding such as stromal collapse are almost always present in close proximity or subjacent to ESC. Previously this phenomenon was termed “papillary syncytial metaplasia,”(23) but it is more degenerative than metaplastic. ESC shows no to minimal proliferative activity.(24)

ESC is characterized by aggregates of stratified eosinophilic cells, often forming small papillary-like tufts lacking a connective tissue core. The syncytial aggregation of pink epithelial cells over clusters on condensed stroma contributes to the pseudo-papillary arrangements. The
cells of ESC are generally oval, and their nuclei have a random, haphazard distribution. The cytoplasm is pale to eosinophilic with occasional vacuoles. Cell borders are indistinct. Overall, the nuclei are cytologically bland, but some cases of ESC show mild nuclear atypia manifested by slight hyperchromasia, pleomorphism, and irregular nuclear outlines. ESC consistently has associated cellular necrotic debris and often has a neutrophilic infiltrate, too. This abnormality can be confused with metaplasia, atypia, or neoplasia. In contrast to metaplastic or neoplastic lesions that largely involve glands, however, ESC is usually limited to surface epithelium.

**Metaplasia.** Endometrial epithelium can show a variety of cytoplasmic changes commonly termed “metaplasia.” These epithelial changes frequently occur in endometria that contain hyperplasia or neoplasia, but they can occur in a variety of other benign conditions, especially polyps. Many disorders previously classified as metaplasia are better termed "change" since they are not true metaplastic transformations of the epithelium.(1)

There are five general types of cytoplasmic change seen in the endometrium.(25) These are squamous, ciliated cell (tubal), eosinophilic, mucinous and secretory (clear cell) change. Eosinophilic cell change often is cytologically related to tubal metaplasia but lacks cilia. Association of eosinophilic cell change with mucinous metaplasia in some cases suggests a relation between the two cell types with eosinophilic change representing a subtype of immature mucinous metaplasia.(26) Tubal metaplasia usually shows immunoreactivity for p16 as well as aberrant expression of some cell cycle proteins, suggesting it has potential to be a premalignant lesion.(27) Progestin therapy or hyperplasia and well-differentiated adenocarcinoma can further enhance various patterns of cytoplasmic change or metaplasia.(28;29) Eosinophilic syncytial change, discussed above along with other features of breakdown and bleeding, is not a metaplasia and is unrelated to the other forms of cytoplasmic transformation.

Like some changes in breakdown such as.artifactual crowding and ESC, metaplastic patterns complicate and confound the interpretation of specimens. Since metaplasia frequently accompanies hyperplasia or well-differentiated carcinoma, separating benign metaplastic changes from atypical changes is of paramount importance. One issue with metaplasia is that these changes, except for secretory change and endocervical-type mucinous change, result in cytoplasmic eosinophilia, a feature shared with gland cells in atypical hyperplasia and low grade
adenocarcinoma as well as the unrelated phenomenon of ESC. The cytologic details of cells in question are the key to making the critical distinction. Metaplastic change should show no atypia. The cells may be pseudostratified in metaplasia, but orientation to the basement membrane is maintained in contrast to atypical epithelium that shows loss of polarity in relation to the underlying basement membrane. The nuclei of metaplasia lack atypia, a feature of atypical hyperplasia (Table 3) and many well differentiated adenocarcinomas. Squamous change presents a different challenge. Squamous change complicates gland patterns because the process can result in crowding of the glands secondary to distention by nests of non-keratinizing squamous cells. In this situation, the other histologic features including cellular atypia of the glandular component and, in the case of carcinoma, confluent gland arrangements, determine the correct diagnosis.

**TERMINOLOGY**

For abnormal endometrium that lacks a specific organic abnormality, selecting the best diagnostic term can be as challenging as the interpretation of the specimen. The gynecologist wishes to know the following:

1) Is there an organic lesion such as a complication of pregnancy, inflammation or a polyp?

2) Is there evidence of active or old breakdown and bleeding?

3) Is there evidence to suggest dysfunctional bleeding?

4) Is there evidence of hyperplasia, atypia, or carcinoma?

When a biopsy is done for DUB, the report should address the presence or absence of morphologic changes of breakdown and bleeding as well as any specific lesions. If the pattern is that of proliferative endometrium with breakdown and if the clinical history is appropriate, the changes can be accurately attributed to anovulatory cycles. A descriptive diagnosis such as “proliferative endometrium with glandular and stromal breakdown” offers a clear morphologic
interpretation of the bleeding pattern that often is sufficient for clinical management. An additional comment indicating that the change is compatible with anovulatory cycles helps to clarify the diagnosis. If the changes show non-menstrual secretory endometrium with breakdown but these are not diagnostic of a defined endometrial phase abnormality, descriptive terms such as “secretory bleeding pattern” communicates the observation of an abnormal yet benign appearance while not assigning definite morphologic etiology. In general a comment regarding the absence of other possible causes of bleeding such as hyperplasia, inflammation, pregnancy, or polyps is most useful in addressing specific clinical concerns.

Occasional biopsies show extensive breakdown and bleeding that largely obscures the cytologic details of the glands and stroma. Although it is usually possible to exclude neoplastic processes in such cases, detailed assessment of the endometrium to determine the underlying pathologic process becomes difficult. Unless the breakdown is clearly menstrual, i.e. reflecting the shedding at the end of a normal ovulatory cycle, breakdown patterns should not be diagnosed as “menstrual.” Instead, it is better to use descriptive diagnoses that reflect the morphologic changes.

Descriptive diagnoses should be used carefully, however. The term “dyssynchronous” endometrium has been used to describe apparent alterations in secretory phase development yet this term does not have a specific connotation or meaning. Its use can be confusing unless there is clear communication between the pathologist and gynecologist regarding its meaning, and I don’t use it. Likewise, the terms “withdrawal” and “breakthrough” should be avoided in pathologic diagnoses because they lack clear definitions in the clinical literature regarding endometrium bleeding. It is best to avoid other vague terms such as “lytic endometrium.”

In summary, the endometrial biopsy showing benign, non-hyperplastic changes presents a distinct group of challenges for the pathologist. A myriad of normal and pathologic processes with varied histology may be encountered. In the absence specific lesions such as endometritis, polyp or hyperplasia, a descriptive evaluation that clearly describes the changes present will help guide the gynecologist in patient management.
### TABLE 1
**POSSIBLE CAUSES OF ABNORMAL SECRETORY PHASE PATTERNS**

- Luteal phase defects
- Persistent corpus luteum (irregular shedding)
- Organic lesions (polyps, secretory hyperplasia, etc.)
- Submucosal leiomyomas
- Intrauterine adhesions
- Inflammation
- Complications of pregnancy
- Progestin effects

### TABLE 2
**HISTOLOGIC FEATURES OF BREAKDOWN AND BLEEDING**

- Stromal “collapse” with cell clusters
- Eosinophilic syncytial change
- Fibrin thrombi
- Nuclear debris at base of gland cells
- Nuclear debris in stroma
- Hemosiderin
- Foam cells
- Stromal fibrosis and hyalinization
TABLE 3
FEATURES OF ENDOMETRIAL EPITHELIAL ATYPIA

- Nuclei enlarged, irregular
- Loss of nuclear polarity
- Chromatin clumping (vesicular appearance)
- Prominent nucleoli
- Cytoplasmic eosinophilia, diffuse or focal
Reference List


BENIGN ENDOMETRIUM: DYSFUNCTIONAL BLEEDING, BREAKDOWN, AND METAPLASIA

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Abnormal Uterine Bleeding:  
*Sentinel of Endometrial Pathology*

- Dysfunctional
- Organic lesions
  - Polyps, Hyperplasia, Carcinoma, etc.
- Atrophy
- Exogenous hormones
- Complications of pregnancy
- Inflammation
- Systemic bleeding disorders
AUB: Most Common

- Dysfunctional bleeding
- Polyps
- Atrophy
Dysfunctional Uterine Bleeding

- Abnormal bleeding with no organic cause
- Pathogenesis:
  A. Anovulatory cycles
  B. Luteal phase abnormalities
    1. Luteal phase defect
    2. Irregular shedding
Anovulatory Cycles

- Follicles develop, but no ovulation with rupture
- Estradiol production leads to endometrial proliferation
- Variable atresia or persistence of follicle
Anovulatory Bleeding

- Follicles involute ➔ No estrogen, withdrawal bleeding
- Follicles persist ➔ Estrogen production, vascular ectasia, breakthrough bleeding
Anovulatory Bleeding Pattern

- Proliferative phase glands and stroma, variable amount
- Glands may have slight disorganization (disordered)
- Glandular and stromal breakdown, focal to diffuse
Proliferative with partial breakdown
Fibrin thrombi and stromal collapse
Proliferative with focal breakdown
Anovulatory bleeding pattern with marked fragmentation
Disordered Proliferative Phase Pattern

- Mildly irregular gland shapes and sizes
- May be result of anovulatory cycles
- Diagnosis often over-used
Luteal Phase Defect

- Inadequate progesterone production from corpus luteum, possibly due to premature regression
- Associated with infertility
- Role in DUB poorly defined
Histologic Features Of LPD

- Histologic date lags by more than 2 days, or possibly
- Irregular maturation, or
- Non-menstrual secretory with breakdown
Secretory with irregular maturation
Secretory with irregular maturation
Secretory bleeding pattern
Causes of Abnormal Secretory Phase Development

- Luteal phase abnormalities
- Organic lesions
  - Polyps, secretory hyperplasia, etc.
- Leiomyomas
- Adhesions
- Chronic inflammation
- Progestin effects
Non-menstrual Breakdown (Bleeding Pattern)

- Pattern of early necrosis of the endometrium
- Specific and unique morphologic features
- Changes along with fragmentation can mimic other lesions
Breakdown with artifactual crowding
Complex hyperplasia
Breakdown And Bleeding

• Stromal “collapse” with clusters
• Nuclear debris (apoptosis)
• Fibrin thrombi
• Eosinophilic syncytial change
• Hemosiderin, foam cells, hyalinized stroma
Eosinophilic Syncytial Change

- Syncytial aggregates of pink epithelium
- Usually along surface epithelium
- Cytologically bland
- Can form pseudo-papillary tufts
Eosinophilic Syncytial Change

- A marker of endometrial breakdown in a variety of conditions, many not hyperplastic or neoplastic
- Regressive change unrelated to “metaplasia”
Focal breakdown with ESC and stromal clusters
Anovulatory bleeding pattern with ESC and stromal clusters
Extensive breakdown with ESC and pseudo-papillary pattern
## Proliferation Comparison

<table>
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<th>Ki-67</th>
<th>pHH3</th>
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<tr>
<td>Gr 1 CA</td>
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</table>

*Ki-67: MIB-1 antibody*

*pHH3 = phospho-histone H2 Ser 28 (mitosis marker)*
Endometrial Cytoplasmic Changes (Metaplasia)

- Squamous
- Ciliated cell (tubal)
- Eosinophilic (pink cell)
- Mucinous
- Secretory (clear cell)
Endometrial Cytoplasmic Change (Metaplasia)

- Usually an estrogenic effect
- May be due to irritation or trauma, e.g., polyp or inflammation
- Often associated with hyperplasia or carcinoma; amplified with progestin therapy
Eosinophilic (Pink) Epithelial Cells

- Atypical hyperplasia
- Adenocarcinoma
- Squamous differentiation
- Ciliated cell change
- Eosinophilic change
- Mucinous change
- Eosinophilic syncytial change (ESC)
Atypical Hyperplasia
Diagnostic Features

• Cytologic atypia, focal or diffuse. Irregular nuclei with chromatin clumping and prominent nucleoli
• Loss of nuclear polarity
• Cytoplasm abundant with dense eosinophilia, focal or diffuse
Atypical hyperplasia
Ciliated/Eosinophilic Cell Change

- Nuclei often round, stratified
- Smaller, uniform nuclei without chromatin changes, nucleoli of atypical cells
- Luminal border usually sharp
Ciliated cell change in simple hyperplasia
Eosinophilic cell change in benign polyp
Mucinous Change

• Variable presentation: from simple endocervical-type epithelium to complex patterns

• Eosinophilic change related to mucinous change in some cases.
Mucinous change in hyperplasia without atypia
Eosinophilic and mucinous change in hyperplasia
Squamous Change
(Squamous Differentiation)

• Seen in polyps, hyperplasia, carcinoma, inflammation
• Often non-keratinizing
• Luminal clusters (morules) gives crowded gland pattern
Benign polyp with squamous metaplasia
Complex atypical hyperplasia with squamous change
Complex atypical hyperplasia with squamous change
Well-differentiated adenocarcinoma with squamous change
Metaplasia
(Cytoplasmic Change)

• Occur in a variety of conditions, often hyperplasia or polyp
• ESC is not related to “metaplasia”
• Evaluate cytologic detail to separate from significant atypia
Common Concerns

• Is the specimen representative and adequate?
• Is hyperplasia, atypia or carcinoma present?
• Abnormal, but benign - what is the best diagnosis?
The Report: Abnormal, Benign and Difficult to Classify

• Exclude other pathology, e.g., polyps, hyperplasia, atypia, etc.
• Minimize comments about metaplasia/cytoplasmic change
• Diagnose descriptively
Descriptive Diagnoses, Examples

• Proliferative with glandular and stromal breakdown
• Abnormal secretory bleeding pattern
• Secretory with irregular maturation

(Avoid: “breakthrough,” “withdrawal,” “dyssynchronous,” “lytic”, etc.)