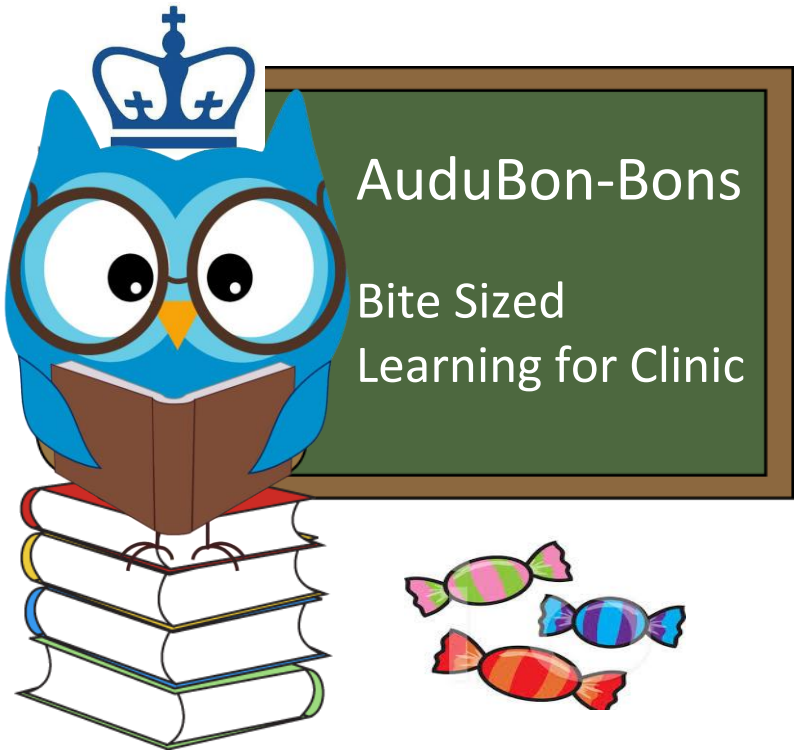
ENDOMETRIAL HYPERPLASIA



Week 78

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Reading Assignment:
ACOG Committee Opinion #631
Endometrial Intraepithelial Neoplasia

LEARNING OBJECTIVES

- To review the most up to date nomenclature for endometrial hyperplasia
- To understand the risk of progression to and concurrent diagnosis of endometrial cancer in patients diagnosed with endometrial intraepithelial neoplasia
- To be able to counsel patients on the management of endometrial intraepithelial neoplasia

CASE VIGNETTE

- A 58 y.o. G2P2 woman presents to your office complaining of vaginal bleeding. She reports having 2-3 episodes of vaginal spotting over the past 1 year. She is worried she could have cancer.

  - She reports her LMP was at age 54.
  - She has no other complaints.

FOCUSED HISTORY

What elements of this patient's history are most relevant?

- **OBHx:** **FT NSVD x 1, FT C/S x 1**
- **GYNHx:** **No menses in ~ 4 years**
  Denies h/o fibroids, ovarian cysts, abnormal paps
  SA with her husband only
- **PMHx:** HTN, **obesity**
- **PSHx:** Laparoscopic appendectomy, cesarean delivery
- **MEDS:** HCTZ
- **ALL:** NKDA
- **SocHx:** 20 pack year smoking history, occasional ETOH, denies use of illicit drugs

PERTINENT PHYSICAL EXAM FINDINGS

What elements of this patient's physical exam are most relevant?

- **Vitals**: BP 149/86, 278lbs, 5'6", **BMI 45**
- **Abd**: **Obese**, non-distended, soft, nontender, **no masses palpated**
- **Pelvic**:
  - **Vulva**: **Normal external female genitalia. No lesions.**
  - **Vagina:** **Atrophic vaginal tissue. No discharge.**
  - **Cervix:** **Parous os. No lesions. No discharge. No CMT.**
  - **Uterus:** **NT. Anteverted. Not enlarged.**
  - **Adnexa:** **NT. No masses palpable.**

DIFFERENTIAL DIAGNOSIS

- After completing a thorough history and directed exam, the patient asks you why she is having this bleeding.
- What are the differential diagnoses for AUB?
- What are the differential diagnosis for PMB?
  - Vaginal or endometrial atrophy
  - Structural lesions
  - Endometrial intraepithelial neoplasia
  - Endometrial cancer

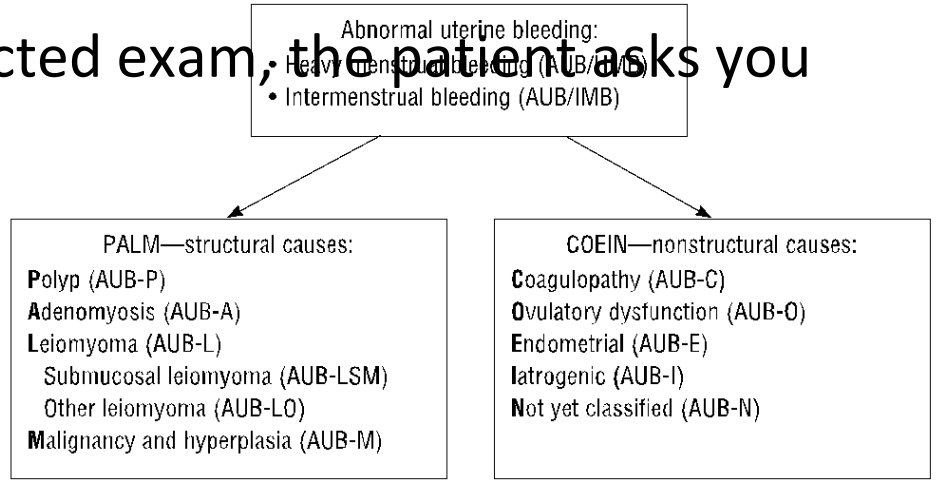


Fig. 1. Basic PALM–COEIN classification system for the causes of abnormal uterine bleeding in nonpregnant reproductive-aged women. This system, approved by the International Federation of Gynecology and Obstetrics, uses the term "abnormal uterine bleeding" paired with terms that describe associated bleeding patterns ("heavy menstrual bleeding" or "intermenstrual bleeding"), a qualifying letter (or letters) to indicate its etiology (or etiologies), or both. Abbreviation AUB indicates abnormal uterine bleeding. (Data from Munro MG, Critchley HO, Broder MS, Fraser IS. FIGO classification system [PALM-COEIN] for causes of abnormal uterine bleeding in nongravid women of reproductive age. FIGO Working Group on Menstrual Disorders. Int J Gynaecol Obstet 2011;113:3–13. [PubMed] [Full Text]) ⇦

EVALUATION

She then asks what the next steps are in diagnosing the cause of her PMB

- **Imaging**
  - Transvaginal ultrasound
  - Saline infusion sonohysterography
- **Endometrial sampling** (See Endometrial Biopsy AudubonBon for more information)
  - Office endometrial biopsy
  - Hysteroscopy directed endometrial sampling (office or operating room)
- **Making the distinction between hyperplasia, precancerous lesions or neoplasia has significant clinical implications**
  - Allows for appropriate interventions
  - Avoid under or overtreatment

PATHOPHYSIOLOGY

- Endometrial hyperplasia is defined histologically as abnormal overgrowth of endometrial glands
- Prolonged, unopposed stimulation of the endometrium by estrogen causes proliferative glandular epithelial changes
- Endometrial hyperplasia is clinically significant because it can be a precursor to adenocarcinoma of the endometrium

RISK FACTORS AND REDUCTION

• Obesity	→	Diet, exercise, weight loss
• Nulliparity and infertility		
• Chronic anovulation	→	Progestin therapy
• Early menarche		
• Late onset of menopause		
• Diabetes	→	Lifestyle modifications, pharmacologic intervention
• Unopposed estrogen therapy	→	Addition of progestins
• Tamoxifen		

ENDOMETRIAL HYPERPLASIA CLASSIFICATION

Currently, there are 2 systems of endometrial pre-cancer nomenclature:

Nomenclature System		Risk of Concurrent Endometrial Ca	Risk of Progression to Endometrial Ca
WHO94 schema: classification of histology based on glandular complexity and nuclear atypia **Endometrial intraepithelial neoplasia schema:** categorized based on pathologic criteria	Simple hyperplasia		1%
	Complex hyperplasia		3%
	Simple hyperplasia with atypia		8%
	Complex hyperplasia with atypia	42%	29%
	Benign (benign endometrial hyperplasia)		
	Premalignant (endometrial intraepithelial neoplasia)	43% (10% high-risk uterine carcinoma)	40%
	Malignant (endometrial adenocarcinoma, endometriod type, well differentiated)	-	-

ENDOMETRIAL INTRAEPITHELIAL NEOPLASIA CRITERIA

Table 1. Diagnostic Criteria for Endometrial Intraepithelial Neoplasia* ⇦

Nomenclature	Topography	Functional Category	Treatment
Benign endometrial hyperplasia	Diffuse	Prolonged estrogen effect	Hormonal therapy, symptomatic
Endometrial intraepithelial neoplasia	Focal progressing to diffuse	Precancerous	Hormonal therapy or surgery
Endometrial adenocarcinoma, endometrioid type, well differentiated	Focal progressing to diffuse	Malignant	Surgery, stage based

*Previously known as atypical endometrial hyperplasia.

Data from Baak JP, Mutter GL, Robboy S, van Diest PJ, Uyterlinde AM, Orbo A, et al. The molecular genetics and morphometry-based endometrial intraepithelial neoplasia classification system predicts disease progression in endometrial hyperplasia more accurately than the 1994 World Health Organization classification system. Cancer 2005; 103:2304–12 *and* Mutter GL. Endometrial intraepithelial neoplasia (EIN): will it bring order to chaos? The Endometrial Collaborative Group. Gynecol Oncol 2000;76:287–90.

ENDOMETRIAL INTRAEPITHELIAL NEOPLASIA CRITERIA

Table 2. Definitions of Endometrial Intraepithelial Neoplasia* Criteria ⇦

Endometrial Intraepithelial Neoplasia* Criteria	Comments
Architecture	Area of glands greater than stroma (volume percentage stroma less than 55%)
Cytology	Cytology differs between architecturally crowded focus and background
Size greater than 1 mm	Maximum linear dimension exceeds 1 mm
Exclude mimics	Benign conditions with overlapping criteria (ie, basalis, secretory, polyps, repair)
Exclude cancer	Carcinoma if maze-like glands, solid areas, or appreciable cribriforming

*Previously known as atypical endometrial hyperplasia.

Data from Baak JP, Mutter GL, Robboy S, van Diest PJ, Uyterlinde AM, Orbo A, et al. The molecular genetics and morphometry-based endometrial intraepithelial neoplasia classification system predicts disease progression in endometrial hyperplasia more accurately than the 1994 World Health Organization classification system. Cancer 2005;103:2304–12 *and* Mutter GL. Endometrial intraepithelial neoplasia (EIN): will it bring order to chaos? The Endometrial Collaborative Group. Gynecol Oncol 2000;76:287–90.

MANAGEMENT

Primary goals in patients diagnosed with endometrial intraepithelial hyperplasia are:

- Ruling out concurrent adenocarcinoma
- Design a treatment plan that can accommodate delayed discovery of an occult carcinoma
- Preventing progression to endometrial cancer

Total hysterectomy is an effective means of treating a biopsy diagnosis of endometrial intraepithelial neoplasia

- Supracervical hysterectomy, morcellation, and endometrial ablation are unacceptable for treatment of endometrial intraepithelial neoplasia.

MEDICAL MANAGEMENT

Is there a role for medical management for our patient?

- Nonsurgical management of endometrial intraepithelial neoplasm is acceptable for certain patient populations:
  - Patients desiring future fertility
  - Patients with medical comorbidities precluding surgical management
- If endometrial intraepithelial neoplasia is present, there is a higher incidence of failure of medical management and subsequent development of cancer

Table 3. Hormonal Treatment for Endometrial Intraepithelial Neoplasia* ⇦

Hormonal Agent	Dosage and Length
Medroxyprogesterone acetate	10–20 mg/d, or cyclic 12–14 days per month
Depot medroxyprogesterone	150 mg intramuscularly, every 3 months
Micronized vaginal progesterone	100–200 mg/d or cyclic 12–14 days per month
Megestrol acetate	40–200 mg/d
Levonorgestrel intrauterine system	52 mg in a steroid reservoir over 5 years

*Previously known as atypical endometrial hyperplasia.

Modified from Trimble CL, Method M, Leitao M, Lu K, Ioffe O, Hampton M, et al. Management of endometrial precancers. Society of Gynecologic Oncology Clinical Practice Committee. Obstet Gynecol 2012;120:1160–75.

Regression of hyperplasia (simple, complex, and atypical) has been observed in 80-90% of patients receiving either of these 2 agents for 3 months.

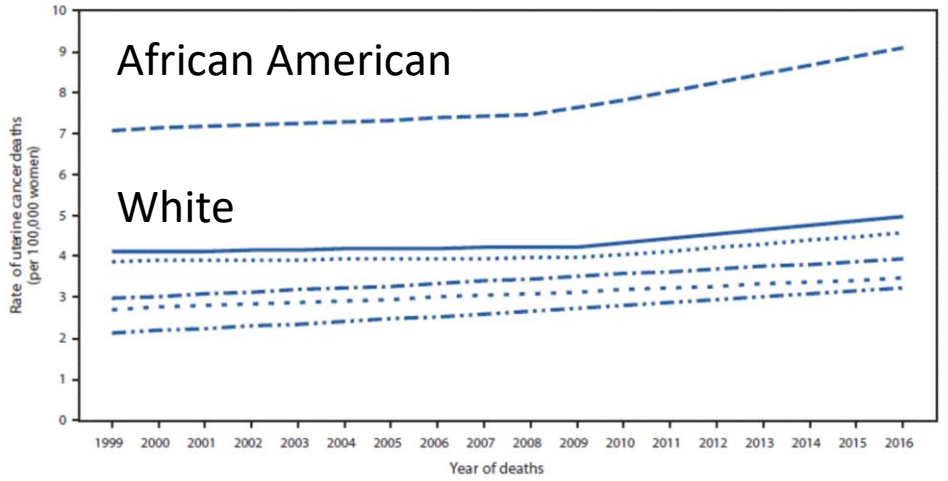
SOCIAL DETERMINANTS OF HEALTH

Black women are approximately **twice as likely to die from uterine cancer** as women in other racial/ethnic groups

Black women are 2x more likely to be diagnosed with distant stage uterine cancer than women of other racial/ethnic groups for each histologic type

Black women are more likely to have aggressive histologic types than other women, including carcinosarcomas, and sarcomas

Uterine cancer death rates, by racial/ethnic group§ — United States, 1999–2016



Source: CDC's National Center for Health Statistics National Vital Statistics System.

Improving access to health care among low-SES women to facilitate earlier diagnosis and optimal treatment may serve to diminish the racial/ethnic difference in endometrial cancer survival.

EPIC .PHRASE

.BBonEndometrialHyperplasia

Description: Endometrial hyperplasia workup and management

Given the presence of [AUB, postmenopausal bleeding, results of transvaginal ultrasound], the need for further evaluation with both imaging and endometrial tissue sampling to determine whether carcinoma or premalignant lesions are present was discussed with the patient.

Recommendations were made to proceed with transvaginal ultrasound and office endometrial biopsy.

Results of the endometrial biopsy were discussed.

A diagnosis of [endometrial intraepithelial neoplasia] was made.

Management options were discussed with patient including expectant vs medical vs surgical management. R/B/A of each were discussed in detail.

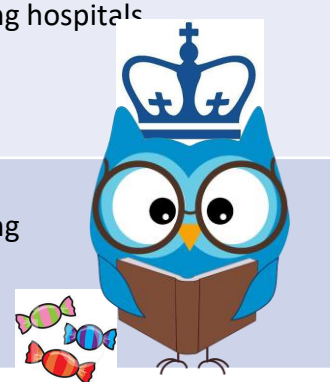
Pt opted for ***.

CODING AND BILLING

- Diagnostic Codes (ICD-10)
  - N93.9 AUB
  - N95 PMB
  - N85.02 Endometrial intraepithelial neoplasia

CODING AND BILLING – NEW PATIENT

HISTORY	EXAM	MEDICAL DIAGNOSIS MAKING	CODE	APPLICABLE GUIDELINES
Problem focused: - Chief complaint - HPI (1-3)	Problem focused: - 1 body system	Straight forward: - Diagnosis: minimal - Data: minimal - Risk: minimal	99201	- Personally provided - Primary care exception - Physicians at teaching hospitals
Expanded problem focused: - Chief complaint - HPI (1-3) - ROS (1-3)	Expanded problem focused: - Affected areas and others	Straight forward: - Diagnosis: minimal - Data: minimal - Risk: minimal	99202	- Personally provided - Primary care exception - Physicians at teaching hospitals
Comprehensive - Chief complaint - HPI (4) - ROS (2-9) - Past, family, social history (1)	Detailed: - 7 systems	Low: - Diagnosis: limited - Data: limited - Risk: low	99203	- Personally provided - Primary care exception - Physicians at teaching hospitals
Comprehensive - Chief complaint - HPI (4+) - ROS (10+) - Past, family, social history (3)	Comprehensive: - 8 or more systems	Moderate: - Diagnosis: multiple - Data: moderate - Risk: moderate	99204	- Personally provided - Physicians at teaching hospitals
Comprehensive - Chief complaint - HPI (4+) - ROS (10+) - Past, family, social history (3)	Comprehensive: - 8 or more systems	High: - Diagnosis: extended - Data: extended - Risk: high	99205	- Personally provided - Physicians at teaching hospitals



CODING AND BILLING – ESTABLISHED PATIENT

HISTORY	EXAM	MEDICAL DIAGNOSIS MAKING	CODE	APPLICABLE GUIDELINES
Expanded problem focused: - Chief complaint - HPI (1-3)	Problem focused: - 1 body system	Straight forward: - Diagnosis: minimal - Data: minimal - Risk: minimal	99212	- Personally provided - Primary care exception - Physicians at teaching hospitals
Expanded problem focused: - Chief complaint - HPI (1-3) - ROS (1)	Expanded problem focused: - Affected area and others	Low: - Diagnosis: limited - Data: limited - Risk: low	99213	- Personally provided - Primary care exception - Physicians at teaching hospitals
Detailed - Chief complaint - HPI (4+) - ROS (10+) - Past, family, social history (3)	Detailed: - 7 systems	Moderate: - Diagnosis: multiple - Data: moderate - Risk: moderate	99214	- Personally provided - Physicians at teaching hospitals
Comprehensive - Chief complaint - HPI (4+) - ROS (10+) - Past, family, social history (2)	Comprehensive: - 8 or more systems	High: - Diagnosis: extended - Data: extended - Risk: high	99215	- Personally provided - Physicians at teaching hospitals

EVIDENCE

- References

  - Armstrong et al. Diagnosis and Management of Endometrial Hyperplasia. Journal of Minimally Invasive Gynecology (2012) 19, 562–571.
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  - The role of transvaginal ultrasonography in evaluating the endome- trium of women with postmenopausal bleeding. ACOG Commit- tee Opinion No. 734. American College of Obstetricians and Gynecologists. Obstet Gynecol 2018;131:e124–9.
  - Vetter MH, Smith B, Benedict J, et al. Preoperative predictors of endometrial cancer at ti of hysterectomy for endometrial intraepithelial neoplasia or complex atypical hyperplasi Am J Obstet Gynecol 2020;222:60.e1-7.