Endometrial Cancer
Biopsy of the endometrium
Evaluation of women of all ages

Barbara S. Apgar, MD, MS
Professor of Family Medicine
University of Michigan Health System
Ann Arbor, Michigan
Cancer of the endometrium is the most common type of gynecologic cancer in the US.

Premenopausal bleeding (irregular menses, intermenstrual bleeding and heavy menstrual bleeding) requires evaluation depending on risk factors.

1-14% of women with postmenopausal bleeding have endometrial cancer.

Postmenopausal bleeding requires prompt and efficient evaluation of the endometrium to exclude or diagnose cancer.
Missed opportunities for primary endometrial cancer prevention

- US women have a 1/38 lifetime chance of developing endometrial cancer.
- Identify women at risk and institute preventive measures to reduce risk.
- Risks we can do something about:
  - Obesity
  - Endometrial hyperplasia

Modesitt SC. Obstet Gynecol 2012:120:989-991
Obesity

- Take aggressive steps to educate women on diet, exercise, bariatric surgery.
- Weight loss is incredibly difficult.
- Strongly consider hormonal protective interventions to regulate menstrual cycles and prevent cancer or hyperplasia.
  - Think OCP’s – 80% reduction endometrial cancer – or Mirena !!!

Goals of endometrial sampling

- To confirm diagnosis of a true premalignant lesion.
- To exclude an associated endometrial carcinoma.
- To reassure that a benign process is present.

Think

Global

or

Focal

Endometrial process
Endometrial Biopsy (EMB)

Disposable suction piston devices have virtually replaced D&C despite little scientific validation

Both EMB and D&C are “blind” endometrial sampling procedures

Goldstein SR. Am J Obstet Gynecol 2009
ACOG statement 2015

- Outpatient endometrial sampling with disposable devices is reliable and accurate for the detection of disease in most cases of endometrial cancer. (Level A Evidence)

- Has become the method of choice for histologic evaluation of the endometrium.

ACOG. Obstet Gynecol 2015;125:1006-25
Outpatient endometrial biopsy with the Pipelle catheter is reliable and accurate for the detection of disease in most cases of endometrial cancer. (Level A)

Hysteroscopic-guided endometrial biopsy remains the gold standard for endometrial cancer diagnosis. (Level A)
Plastic endometrial aspirator
Possible endometrial biopsy findings

- Benign: Proliferative, secretory or atrophic endometrium
- Inactive endometrium
- *Tissue insufficient for evaluation*
- *No endometrial tissue seen*
- Simple or complex hyperplasia without atypia
- Simple or complex hyperplasia with *atypia*
- Endometrial adenocarcinoma
Should we do EMBs?

- Sampling failure (0-54%).
  - Inadequate sample.
    - Endometrium is thin or atrophic (68% in postmenopausal women)
  - Inability to perform the biopsy.
    - Cervical stenosis, pain.

- Low sensitivity for detecting polyps and submucosal fibroids.

- High sensitivity for detecting endometrial cancer and hyperplasia *when a global process is present.*

Issues with use of EMB

- Stenotic os

Apgar, Brotzman, Spitzer
Risk factors for developing endometrial cancer after benign sampling

- Factors independently associated with subsequent endometrial cancer.
  - Personal hx colorectal cancer
  - Endometrial polyp
  - Morbid obesity

- Presence of one or more factors, increases risk by 8 times.

- 25% of patients with endometrial cancer had a previous benign EMB/D&C.

Torres et al. Obstet Gynecol 2012;120:998-1104
Women had Pipelle sampling before hysterectomy

Uterus opened to study gross extent of disease.

- Of the 11 cases (17%) where cancer was missed:
  - 3 occupied < 5% of the surface area.
  - 4 were < 25% of the surface area.
  - 4 were < 50% of the surface area.

- In only 40% of the cancer cases did the tumor occupy > 50% of the uterine cavity surface. (Pipelle detected all the malignancies)

Does D&C detect focal lesions?

- 900 women had D&C followed by hysteroscopy.
- 80% had uterine pathology and 98% of the pathologic lesions showed a focal growth pattern at hysteroscopy.
- 87% of the women with focal lesions had whole or parts of lesions remaining after D&C.
- Agreement between D&C and final diagnosis was excellent (94%) in women who had a “global” process.

Intrauterine lesions missed when only D&C performed

- Blind D&C followed by hysterectomy  n=397
  - 159 fibroids missed.
  - 63 endometrial polyps missed.
  - 4 cases of complex hyperplasia missed.
  - 5 cases of focal endometrial cancer in the tubal cornua missed.

- Missed 62.5% of major intrauterine disease.

Reproductive-aged women and endometrial cancer
24 year old with 4 menses/year that are all very heavy and can last 14 days. Not able to conceive. BMI 50. Not had evaluation for either heavy menstrual bleeding or facial hirsutism. Never used contraception.

What is the next step?
Age is important risk factor for endometrial cancer in young women

- Are more likely to be obese, nulliparous and have well-differentiated endometrial histology and lower stage disease.

- Risk factors: increasing BMI, nulliparity and irregular menses.

- *Risk is increased by as much as 22-fold in women < age 45 whose BMI > 35.*

Endometrial evaluation of adolescents

  - 0.2/100,000 women.
  - Typical scenario includes 2-3 years of AUB and obesity.
- Medical treatment first after thorough evaluation of co-morbid condition(s) or other causes.
- EMB only if risk factors present.
Endometrial evaluation ages 19-36

- Risk of endometrial cancer.
  - Ages 20-34: 1.6%.
  - Ages 35-44: 6.2%.

- Risk factors in women ≤ 40 years.
  - Nulliparity.
  - BMI > 30.
  - Irregular menses.
  - FH endometrial cancer.
Endometriar evaluation ages 19-36

- *Medical treatment first.*
- If no response and obesity, proceed with endometriar assessment.
- EMB non-diagnostic or hyperplasia but cancer is not present, proceed with SIS or hysteroscopy with further sampling.
Endometrial evaluation ages 40 to menopause

- Incidence of endometrial cancer:
  - Ages 20-34: 1.6%.
  - Ages 35-44: 6.2%
  - Ages 40-50: 14-24 cases/100,000.

- More advanced stage disease.
- Lower degree of tumor differentiation.
- Worse prognosis.
- EMB before medical treatment.
Premenopausal women with AUB

- Consideration of age-related factors.
- *Ultrasound measurement of endometrial thickness has no diagnostic value and should not be performed (don’t request it).*
  - Literature unclear about imaging for other indications.
- Endometrial biopsy should be based on symptoms and clinical presentation.

Postmenopausal Bleeding (PMPB)

Women who present with clinical signs of menopause (with or without FSH levels) and then bleed after 1 year of no bleeding must be approached as: “having endometrial cancer until proven otherwise”

*Ages 70-74: 87 cases/100,000.*
64 year old obese postmenopausal women has had vaginal bleeding/spotting for 3 months. No pain. Denies other bleeding after LMP 14 years ago. No hormones. Negative Pap/HPV 2 years ago. Hypertension and hyperlipidemia, treated.

What is the next step?
Postmenopausal bleeding (PMPB) incurs a 64-fold increased risk for endometrial cancer.

- D&C
- Disposable EMB instruments
- Hysteroscopy
- Sonohysteroscopy (SIS)
- Transvaginal ultrasound
When transvaginal ultrasound (TVUS) is performed for the initial evaluation of women with PMPB and an endometrial thickness of $\leq 4 \text{ mm}$ is found:

- *Endometrial biopsy is not required.* (Level B evidence)

- Incidence of cancer = 1/1000.
ACOG statement 2015

- Endometrial thickness > 4mm or an inability to adequately visualize thickness in a woman with PMPB should trigger alternative evaluation.

- Prevalence of polyps or fibroids = 50%.

- Endometrial biopsy, sonohysteroscopy (SIS), office hysteroscopy.

ACOG. Obstet Gynecol 2015;125:1006-25
Is a D&C still used?

- No longer acceptable as standard of care for endometrial assessment or to be used as the only surgical treatment for AUB.
  - Unless used with hysteroscopy or ultrasound guidance.
- Important to evaluate focal lesions and D&C cannot do that (neither can EMB).
Can TVUS replace D&C?

- 394 women with PMPB had TVUS and D&C.
  - 86% had 10 year follow-up.

- No women with endometrial thickness ≤ 4 mm diagnosed with endometrial cancer.

- An endometrial thickness ≤ 4mm has a risk of cancer = 1 in 917.

Can TVUS exclude cancer?

An endometrial thickness > 4 mm is not diagnostic of any particular pathology and cannot be relied on to exclude cancer.
65 year old postmenopausal woman had 1 week of bleeding a month ago. TVUS showed an endometrial thickness of 4 mm with no abnormal findings. No further diagnostic testing done. She returns 6 months later after another episode of vaginal bleeding.

What is the next step?
ACOG statement 2015

Persistent or recurrent uterine bleeding should prompt a *histologic evaluation* of the endometrium regardless of endometrial thickness. (Level 2 evidence)

Transvaginal ultrasound

◆ If EMB sample is insufficient.
  ◆ No further evaluation is necessary if subsequent TVUS shows an endometrial thickness \( \leq 4 \text{mm} \) in a woman with PMPB.
  ◆ Incidence of endometrial cancer rare but not impossible.

ACOG Comm Opinion #440, 2009
Endometrial polyps in symptomatic women

- Can be found in 13-50% of symptomatic women who have imaging studies.
- Common cause of heavy menstrual bleeding resistant to medical tx in premenopausal women.
  - 18% are malignant in premenopausal women
- Postmenopausal women with bleeding.
  - 5% have malignant polyps.

Cruz Lee S et al. Obstet Gynecol 2010;116:1197-1205
Saline infusion sonohysteroscopy (SIS)
van Dongen H et al.  BJOG 2007;114:664-675

- Subset of TVUS - Why do it?.
  - An adequate endometrial stripe is not seen on TVUS.
  - When the endometrial stripe is seen but not sufficiently thin.
  - When endometrial stripe is thicker than expected.

- Sensitivity/specificity of SIS = 0.95/0.88
- Sensitivity/specificity of hysteroscopy = 0.94/0.89
Why does TVUS miss intracavitary lesions detected by SIS?

◆ Focal lesions may not be visualized on TVUS because of a collapsed endometrial cavity.

◆ Endometrial polyps may be missed on TVUS because of compression and resultant flattening and conformation to the shape of the cavity.

Bradley LD. Menopause 2011;18:425-433
Diagnostic hysteroscopy (DH)

- Perform if SIS unavailable.
- Consider DH or SIS to accurately diagnose intracavitary benign pathology or focal lesions.
  - Endometrial cutoff of 5mm is inaccurate for detecting benign pathology in women with PMPB.
- Failure rate of office hysteroscopy = 4-10%
- Failure rate of SIS = 7%

van Dongen H et al. BJOG 2007;114:664-675
Skaznik-Wiliel ME. Menopause 2010;17;104-108
Diagnostic hysteroscopy (DH)

◆ Mostly performed in the office.
◆ Accurate diagnosis directs treatment at specific pathology and avoids needless surgery.
◆ Likelihood of cancer diagnosis after negative DH is 0.4%.

van Dongen H et al. BJOG 2007;114:664-675
Bradley LD. Menopause 2011;18:425-433
The End.....

Thanks all!