Too much, too little, too late: Abnormal uterine bleeding

The Questions

• Too much (& too early or too late)
  – Differential and approach to work-up
  – Does she need an endometrial biopsy (EMB)?
  – Does she need an ultrasound?
  – How do I stop peri-menopausal bleeding?
  – Isn’t it due to the fibroids?

• Too fast: She’s hemorrhaging—what do I do?

• Too little: A quick review of amenorrhea
Case 1

A 46 yo G3P2T1 reports her periods have become increasingly irregular and heavy over the last 6-8 months. Sometimes they come 2 times per month and sometimes there are 2 months between. LMP 2 months ago. She bleeds 10 days with clots and frequently bleeds through pads to her clothes. She occasionally has hot flashes. She also has diabetes and is obese.

1. What term describes her symptoms?
2. Physiologically, what causes this type of bleeding pattern?
3. What is the differential?

Q1: In addition to a urine pregnancy test and TSH, which of the following is the most appropriate test to obtain at this time?

1. FSH
2. Testosterone & DHEAS
3. Serum beta-HCG
4. Transvaginal Ultrasound (TVUS)
5. Endometrial Biopsy (EMB)
Terminology: What is abnormal?

- **Normal**: Cycle = 28 days +/- 7 d (21-35); Length = 2-7 days; Heaviness = self-defined
- **Too little bleeding**: amenorrhea or oligomenorrhea
- **Too much bleeding**: Menorrhagia (regular timing but heavy (according to patient) OR long flow (>7 days)
- **Irregular bleeding**: Metrorrhagia, intermenstrual or post-coital bleeding
- **Irregular and Excessive**: Menometrorrhagia
- Preferred term for non-pregnant bleeding issues = Abnormal Uterine Bleeding (AUB)
  - Avoid “DUB” - dysfunctional uterine bleeding.

Pathophysiology: Anovulatory Bleeding

**Bricks & Mortar**

**Estrogen** = Bricks, build endometrium

**Progesterone (P)** = Mortar, stabilizes, only have P if ovulate

**Normal menses**: Withdrawal of P causes wall to fall down, all at once (orderly bleed)

**Anovulation**: No P so when wall grows too tall, it falls. It is heavy when wall is tall. Bricks can also fall intermittently & incompletely – irregularly, irregular
**Differential: AUB**

**Step 1: Pregnant?**

<table>
<thead>
<tr>
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<th>Not Pregnant</th>
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<tbody>
<tr>
<td>• Ectopic</td>
<td>• Anovulation ***</td>
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<tr>
<td>• Spontaneous Abortion</td>
<td>• Anatomic/structural **</td>
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<tr>
<td>• Threatened Abortion</td>
<td>• Neoplastic *</td>
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<td>• Molar Pregnancy</td>
<td>• Infectious</td>
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<tr>
<td>• Trauma</td>
<td>• Iatrogenic</td>
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<tr>
<td>• Some non-pregnant causes</td>
<td>• Non-gynecologic</td>
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* = Most likely for this patient

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**Causes of Anovulation**

**Physiologic**
- Peri-menarche/Peri-menopause
- Obesity

**Hyperandrogenic**
- PCOS

**CNS**
- Hypo/Hyper Thyroid

**Iatrogenic**
- Anorexia/Over-exercise
### Reference: Causes of Anovulation

<table>
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<th>Physiologic</th>
<th>Hyperandrogenic</th>
<th>CNS</th>
<th>Iatrogenic</th>
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<td>Pituitary adenoma</td>
<td>Levonorgestrel</td>
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<tr>
<td>Peri-menarche+</td>
<td>Adult-onset congenital adrenal</td>
<td>(prolactin-secreting)*</td>
<td>IUD#</td>
</tr>
<tr>
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<td>hyperplasia+</td>
<td>Neuroleptic agents (via</td>
<td>Progestin</td>
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<td>Breast-feeding*</td>
<td></td>
<td>increased prolactin)*</td>
<td>injection*#</td>
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<tr>
<td>Obesity (via insulin effect in ovary)+</td>
<td></td>
<td>Hypo or hyper thyroid (* or +)</td>
<td>Progestin implant#</td>
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<td></td>
<td></td>
<td>Hypothalamic (stress,</td>
<td>Combined hormonal contraception#</td>
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<td>anorexia)*</td>
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*Typically amenorrhea
#
Typically spotting/light irregular bleeding
*
Typically irregular heavy bleeding (q 1.5-6 mos)

### Reference: AUB Differential

- **Not Pregnant**
  - Anovulation
  - Anatomic
  - Neoplastic
  - Infectious
  - Non-Gynecologic

- **Uterus:** Myoma, polyp, adenomyosis, atrophy
  - Cervix: polyp, atrophy, trauma
  - Vagina: atrophy, trauma
- **Uterus:** Hyperplasia, cancer
  - Cervix: Dysplasia, cancer
  - Ovary: hormone producing tumor
- **Uterus:** Endometritis, PID
  - Cervix: Cervicitis
  - Vagina: Vaginitis (eg Trich)
- **Coagulopathy** (vWD), severe renal or liver dz, GI or GU source
### Initial Work-up: Menometrorrhagia

- **Always:** Urine pregnancy
- **Usually:** TSH
- **Maybe:** Hct, r/o coagulopathy
- **Maybe:** EMB (Endometrial Biopsy)
- **Maybe but later:** Transvaginal Ultrasound
- **Usually not necessary:** FSH, LH, Testosterone, Estradiol

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### Does she need an EMB?

**Endometrial Cancer Facts**

- 4th most common cancer in women; average age 61 but 25% occur in premenopause
- 10% of post-menopausal women with bleeding have cancer
- Presents at early stage with bleeding: rare in the absence of bleeding. Vast majority effectively treated with simple hysterectomy
- Risk factor = Increased estrogen (long h/o anovulation e.g. PCOS, obesity). Protective = smoking, OCP’s
The Problem

- Irregular bleeding is common
- Endometrial cancer is relatively common
- Risk prediction models are not useful
- Little evidence to guide us regarding when to do EMB
- ACOG guidelines (expert opinion) recommend biopsy in MANY women

ACOG, July 2012

When is endometrial tissue sampling indicated in patients with abnormal uterine bleeding and how should it be performed?

The primary role of endometrial sampling in patients with AUB is to determine whether carcinoma or premalignant lesions are present, although other pathology related to bleeding may be found. Endometrial tissue sampling should be performed in patients with AUB who are older than 45 years as a first-line test (see Fig. 2). Endometrial sampling also should be performed in patients younger than 45 years with a history of unopposed estrogen exposure (such as seen in obesity or PCOS), failed medical management, and persistent AUB (3).

ACOG Practice Bulletin 128, Diagnosis of AUB in Reproductive-Aged Women
Perimenopause

- Averages 4 years
- 12% suddenly stop menstruating
- 18% have longer, heavier menses
- 70% have short, irregular menses

Should we therefore perform EMB on all but 12% of women?

The Evidence...

- One prospective cohort study of 1000 women to test less aggressive EMB Clinical Pathway
- All eligible for biopsy using ACOG guidelines. Only biopsied those that were post-menopausal or had at least 1 risk factor (n=570)
- No cancers/hyperplasia in 2 yrs f/u in those that weren't biopsied. (under-powered to answer this question)

Dunn, Reprod Med. 2001 Sep;46(9):831-4
A Rational Approach to EMB

- **Natural history**: Endometrial cancer takes many years to develop progressing from no atypia to atypia prior to invasion. We have time to detect it.
- **Bleeding pattern cues**: Cancer & hyperplasia present most commonly with menometrorrhagia, sometimes with intermenstrual bleeding. Rarely with regularly-timed menses.
- Progestins (IUD, progestin-only pill) have been shown to treat hyperplasia and cancer.

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A Rational Approach to EMB

- **Post-Menopause**: ALL women WITH ANY BLEEDING (except 4-6 months after starting HRT)
- **Recent onset irregular bleeding**: Consider treating first and if bleeding normalizes, no need EMB
- **>50**: All women with recurrent, irregular bleeding (consider not doing if periods light and spacing out)
- **45-50**: Recurrent irregular bleeding plus ≥1 risk factor OR > 6 mos menometrorrhagia
- **<45**: Long history (>2 yr? >5yr?) of untreated anovulatory bleeding (eg PCOS)
A Rational Approach to EMB (cont’d)

Other reasons: Pap with atypical glandular cells or endometrial cells (ie if pap not done at time of menses).

EMB is not perfectly sensitive so further evaluation mandatory if:
1. Persistent AUB after negative EMB
2. Persistent AUB after 3-6 months of medical therapy

Do all women with AUB need an ultrasound?

Although TVUS is the best imaging choice for pelvic pathology (ie better than MRI, CT)….

• 80% with heavy menstrual bleeding have no anatomic pathology
• Incidental findings such as functional ovarian cysts and small fibroids (~50%) are often found leading to anxiety and unnecessary treatments
• SO....treat first, TVUS if treatment fails
What about U/S instead of EMB for post-menopausal bleeding?

Transvaginal Ultrasound

• Measure endometrial stripe
• Abnormal = >4 mm (or 5)
• Non-specific: myomas, polyps also cause thick EM
• Operator skill mandatory
• NOT USEFUL PRE-MENOPAUSE

TVUS vs EMB to Detect Cancer
(in post-menopausal women)

<table>
<thead>
<tr>
<th></th>
<th>TVUS</th>
<th>EMB</th>
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<tr>
<td>Sensitivity</td>
<td>96%</td>
<td>94%</td>
</tr>
<tr>
<td>Specificity</td>
<td>61%</td>
<td>99%</td>
</tr>
<tr>
<td>NPV</td>
<td>99%</td>
<td>99%</td>
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Further w/u necessary ? <5%

Can offer patient choice as long as either is quickly available and patient understands she may need EMB after U/S
Q1: In addition to a urine pregnancy test and TSH, which of the following is the most appropriate test to order at this time?

1. FSH
2. Testosterone & DHEAS
3. Serum beta-HCG
4. Transvaginal Ultrasound
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A 46 yo G3P2T1 reports her periods have become increasingly irregular and heavy over the last 6-8 months. Sometimes they come 2 times per month and sometimes there are 2 months between. LMP 2 months ago. She bleeds 10 days with clots and frequently bleeds through pads to her clothes. She occasionally has hot flashes. She also has diabetes and is obese.

EMB=“Disordered Proliferative”. How do I stop the bleeding?

**Medical**
- NSAID’s
- Tranexamic Acid
- Oral E+P
- E+P patch, ring
- HRT (lower dose E+P)
- HRT patch
- Oral Progestin
- Progestin IUD
- IM Progestin
- GnRH agonist

**Surgical**
- Endometrial ablation
- (D&C/Hysteroscopy)
- Hysterectomy (failed medical management)

Disordered proliferative= Anovulation
**Non-hormonal Treatment: NSAID’s**

- 5 days around the clock (eg 600 mg tid)
- Many dosages and types proven effective in multiple RCT’s to decrease bleeding by ~40%
- Use alone or with other therapies

  DON’T FORGET NSAIDs!

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**First Line Hormonal Treatments**

- **First choice:** Levonorgestrel IUD
  - >80% reduction in blood loss, decreased cramping, prevents/treats hyperplasia, highly effective birth control
  - Very few contraindications to using
  - Blood loss and satisfaction comparable to ablation, satisfaction comparable to hyst.
- **2nd choice:** combined contraceptives (pill, patch, ring) or progestin injection
  - Proven to decrease irregular peri-menopausal bleeding
  - Any type ok, 20 mcg preferred for women >40
  - Estrogen contraindications: smokers>35, HTN, complicated DM, multiple RF for CAD, h/o DVT, migraines
Second Line Hormonal Options

• **Cyclic Progestins:**
  – Less effective than NSAID’s and Levo IUD
  – 21-day therapy more effective than 10-day but poorly tolerated

• **HT (post-menopausal dosing):**
  – More difficult to gain cycle control compared with OCP
  – Same contraindications as Combined Hormonal Contraception

Transexamic Acid

• Anti-fibrinolytic; available in Europe for many years-
  available in US 2011
• Expensive $170 per cycle
• In RCT’s, more effective than NSAID, cyclic provera.
  – Less effective than Mirena. Improves QOL by 80% by 3rd cycle
• Dose: 2 tabs tid for 5 days (3900mg)
• Risks: Theoretic risk of VTE. No increase in large studies.
  Contraindicated in those with history of or risk factors for VTE. Unknown if safe in conjunction with CHC.
• Side effects: Minimal
Surgical Treatments

- **D&C, Hysteroscopy:**
  - Not really a treatment. Temporary reduction in bleeding. Diagnostic, not curative (except if polyp removed).

- **Endometrial Ablation**
  - Reduces but doesn’t eliminate menses
  - ~25% repeat ablation or hyst in 5 years
  - Must rule out cancer first
  - Can’t be done in >12 week uteri or for women who want fertility

Perimenopausal/Anovulatory Bleeding: Summary

- R/o pregnancy, thyroid dz
- EMB if meets criteria
- Treat first as if anovulatory bleeding:
  - NSAID’s +
  - Hormones (Levo IUD, CHC, DMPA)
- If persists:
  - U/S to check for anatomic causes (and EMB if not already done)
  - Discuss surgical options for bleeding refractory to medical management.
Case 2: Is it the fibroids?

Same history as Case 1 except she has fibroids....

A 46 yo G2P2 woman presents stating that her fibroids are causing irregular bleeding.

She has a known fibroid uterus and complains of increasingly irregular and heavy periods. Sometimes they come 2 times per month and sometimes there are 2 months between. LMP 2 months ago. She bleeds 10 days with clots and frequently bleeds through pads to her clothes. She occasionally has hot flashes. She also has diabetes and is obese.

On exam, her uterus is 16 weeks size and irregular.

Fibroids......

• Very common → 80% of hysterectomy specimens (done for any reason) and ~75% have on U/S at age 50.
• 2-3 fold higher incidence in black women
• About 50% are asymptomatic
• Grow slowly until menopause and then decrease by ~50% (can still cause bleeding post-menopause)
Fibroid Symptoms

- **Bleeding**
  - Usually normal or menorrhagia (heavy but regular). Fibroids stretch endometrium = more bleeding
  - Occasionally menometrorrhagia if submucous or intracavitary (Fibroids distort endometrium so it can’t ever be stable = constant bleeding)
- **Pressure** (not pain)
- **Dysmenorrhea**

Is the bleeding due to the fibroids?

- Fibroids are common in later 40s
- Anovulation is common in later 40s
- The increased bleeding seen with fibroids is typically due to increased volume or distortion of the endometrium
- **Therefore**: Decrease the amount of endometrium by treating as anovulatory bleeding. This often works.
### AUB with Known Fibroids: Work-up and Treatment

- R/o cancer (using “rational emb algorithm” and pregnancy (don't blame fibroids for the bleeding)
- NSAID’s and hormones
- If no better, blame the fibroids!
- +/- Lupron--as a bridge to menopause or pre-op to shrink to obtain less invasive route of hysterectomy
- Surgical therapies (hysteroscopic resection if <3 cm, myomectomy, hysterectomy, UAE)

### Hysterectomy

- Very high patient satisfaction (90%) (higher than ablation)
- Improved quality of life, sexual satisfaction and decreased pain
- Increased long term risks of prolapse, incontinence
Uterine Artery Embolization

- Benefits: 40% decrease in size, 75-90% improved bleeding
- Unknown: Will they re-grow? In 5yr f/u of RCT, 25% had hysterectomy
- Not for: women who want fertility
- A “major” non-surgical procedure:
  - Requires hospitalization for pain control,
  - ~2 weeks to return to full activities (due to pain and fever)
  - Risks: emergent hyst (1-2%), 5% expel myoma through cervix, 40% have fever

Case 3... Too Fast

41 year old woman presents with dizziness and heavy vaginal bleeding for 2 weeks straight.

Prior to this, occasional irregular periods but nothing like this!

Hemoglobin=9
Acute Menorrhagia Treatment

ABC's and Stop the bleeding!
• Consider ED for transfusion
• Estrogen—2-4 OCPs (30-35 mcg E2)
  – Increases fibrinogen, factors V, IX, platelet aggregation.
  “Covers” denuded areas in uterus
  – Oral as effective as IV (so use oral)
• Give with anti-emetic
• Small RCT suggests high-dose provera may be effective as well, 20mg tid
• If not effective, options: D&C, Foley bulb tamponade, emergency hysterectomy

OCP Taper

• Don’t want to give 2-4 OCP’s per day and then stop suddenly b/c will have large withdrawal bleed
• Taper: 4 x 4 days, 3 x 4 days, 2 x 4 days then 1 per day for 1-2 months (66-96 pills required).
• Instruct not to take placebos and give at least 3 packs of pills at once.
• Give with anti-emetic, split bid (i.e. 2 bid rather than 4 all at once)
What about too little bleeding?

Seven questions in evaluation of 2° amenorrhea

1. Pregnant?
2. Excessive hair growth or acne? → PCOS
3. Overweight? → Obesity-induced anovulation
4. Breast secretions? → Hyperprolactinemia
5. Very thin, over-exercise, stress? → Functional hypothalamic amenorrhea
6. Hot flashes? → Premature ovarian failure
7. Pregnant recently complicated with infection or uterine surgery (D&C)? → Asherman’s syndrome

WORK-UP: Amenorrhea

• **Always:**
  – Urine pregnancy test.
  – If Neg: TSH & PLN
• **If hot flashes:**
  – FSH
• **If hirsute/obese:**
  – Usually no further testing needed. ([If deep voice or clitoromegaly: testosterone. If family history hirsutism or onset at puberty: 17 OH-P])**
## Reference: Progestin Challenge Test

- **Progestin challenge test**: (10 mg Provera x 10 days)
  - Bleeding after confirms endogenous estrogen is present
  - Distinguishes hypothalamic amenorrhea (no bleeding or just spots) from PCOS (full withdrawal bleed)
- **Estrogen challenge test**: (Premarin 2.5 mg qd x 3 wks then Provera x 10 days) distinguishes hypothalamic amenorrhea (full withdrawal bleed) from Asherman’s (no bleeding or just spots)

## Amenorrhea Treatment

1. **PCOS** → Protect the endometrium! (from hyperplasia due to unopposed E2) → combined contraceptives, DMPA, LNG IUD
2. **Obesity induced anovulation** → same
3. **Hyperprolactinemia due to microadenoma** → OCPs or nothing, Bromocriptine if desires pregnancy or to treat sxs
4. **Functional hypothalamic amenorrhea**-- protect the bones! (from lack of E2) → estrogen-containing contraceptives
5. **Premature ovarian failure** → same
6. **Asherman’s syndrome** → Hysteroscopy
Conclusions

- **Diagnosis:** consider anovulation even in women with fibroids.
- **Work-up:** Always rule out pregnancy. Usually: TSH, PLN, ?HCT, ?EMB, TVUS if initial treatment fails.
- **Treatment:** all bleeding treated similarly; NSAID's plus hormones. Consider other causes and treatments if this doesn't work. Prevent hyperplasia with progestin-dominant hormones.
- Persistent abnormal bleeding requires continued work-up even if EMB and/or ultrasound are negative.