Too much, too little, too early, too late, too fast: Abnormal Uterine Bleeding

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The Questions

- Too much (& too early or too late)... Menometrorrhagia
  1. Differential and approach to work-up.
  2. Does she need an EMB?
  3. Does she need an ultrasound?
  4. How do I stop peri-menopausal bleeding?
  5. Isn’t it due to the fibroids?
- Too fast: She’s hemorrhaging—what do I do?
- Too little: A quick review of 2nd amenorrhea
- Too late: pregnant and bleeding

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.

Q1: In addition to a 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
5. Endometrial Biopsy

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

- **Normal**: Cycle = 28 days ± 7 days (21-35); Length = 2-7 days; Heaviness = self-defined
- **Too little bleeding**: amenorrhea or oligomenorrhea
- **Too much bleeding**: Menorrhagia (regular timing but heavy 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, stabilize it, 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. Bleed is heavy because wall is tall. Bricks can also fall intermittently & incompletely i.e. irregularly irregular

Differential: AUB

**Step 1: Pregnant vs Not**

*Pregnant*  
- Ectopic  
- Spontaneous Abortion  
- Threatened Abortion  
- Molar Pregnancy  
- Trauma  
- Some non-pregnant causes

*Not Pregnant*  
- Anovulation ***  
- Anatomic/structural **  
- Neoplastic *  
- Infectious  
- Iatrogenic  
- Non-gynecologic

Causes of anovulation

- **Physiologic**  
- Hyperandrogenic  
- CNS  
- Iatrogenic

- **PCOS**  
- Hypothyroidism  
- Obesity  
- Addiction/Over-exercise

* = Most likely for this patient
Reference: Causes of anovulation

- Physiologic
  - Pregnancy
  - Peri-menarche
  - Peri-menopause
  - Breast-feeding
  - Obesity (via insulin effect in ovary)

- Hyperandrogenic
  - PCOS

- CNS
  - Pituitary adenoma (prolactin-secreting)
  - Neuroleptic agents (via increased prolactin)
  - Hypo or hyper thyroid
  - Hypothalamic (stress, anorexia)

- Iatrogenic
  - Levonorgestrel IUD (Mirena)
  - Depo-provera
  - Nexplanon
  - Implanon
  - OCP

Reference: AUB Differential

- Not Pregnant
  - Anovulation
    - Anatomic
    - Neoplastic
    - Infection
    - 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

Reference: New Schema for AUB diagnosis and terminology

- Abnormal uterine bleeding:
  - Heavy menstrual bleeding (HUB/RMB)
  - Intermenstrual bleeding (AIM/BIM)

- PALM-structural causes:
  - Polyp (AUB-P)
  - Adenomyosis (AUB-A)
  - Leiomyomas (AUB-L)
  - Submucous leiomyoma (AUB-SLM)
  - Other leiomyomas (AUB-L)
  - Myoma and heterotopia (AUB-M/H)

- COEIN—non-structural causes:
  - Coagulopathy (AUB-C)
  - Ovulatory dysfunction (AUB-O)
  - Endometrial (AUB-E)
  - Idiopathic (AUB-I)
  - Not yet classified (AUB-N)

What about heavy AND irregular?

PALM- COEIN

“PALM-COEIN”

FIGO (Federation International Gyn & Ob)

Initial Work-up: menometrorrhagia

- Always: Urine pregnancy
- Usually: TSH
- Maybe: Hct, r/o coagulopathy
- Maybe: EMB
- Maybe but later: Transvaginal Ultrasound
- Usually not necessary: FSH, LH, Testosterone, Estradiol
Does she need an EMB?

Endometrial Cancer Facts

- 4th most common cancer in women
- Average age 61 but 25% occur pre-menopausally
- 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 hyst
- 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 inopposed estrogen exposure (such as seen in obesity or PCOS), failed medical management, and persistent AUB (3).

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, J 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 as they are not under hormonal control.
- Progestins (IUD, progestin-only pill) have been shown to treat hyperplasia and cancer

A Rational Approach to EMB

**Post-Menopause**: ALL women WITH ANY BLEEDING (except 4-6 months after starting HRT)

**Recent onset irreg blding**: Consider treating first and if blding 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-meno blding?
Transvaginal Ultrasound
- Measure endometrial stripe
- Abnormal= >4 mm (or 5)
- Non-specific: myomas, polyps and hyperplasia all 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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<tbody>
<tr>
<td>Sensitivity</td>
<td>96%</td>
<td>94%</td>
</tr>
<tr>
<td>Specificity</td>
<td>61%</td>
<td>99%</td>
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<tr>
<td>NPV</td>
<td>99%</td>
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Further w/u necessary 40-50% ? <5%

Can offer patient choice as long as either is quickly available and patient understands she may need EMB after U/S

EMB=“B9 Proliferative”. How do I stop the bleeding?

Medical
- NSAID’s
- Tranexam Acid
- Oral E+P (OCP)
- E+P patch, ring (Evra, Nuvaring)
- HRT (lower dose E+P)
- HRT patch (Combi-patch)
- Oral Progestin
- Progestin IUD (Mirena)
- IM Progestin (DMPA)
- GnRH agonist (Lupron)

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

B9 Proliferative= Anovulation
Non-hormonal treatment: NSAID's

- 5 days around the clock
- Many dosages and types proven effective in multiple RCT's to decrease bleeding by ~40%
- Use alone or with other therapies

DON'T FORGET NSAID's!

Tranexamic Acid (Lysteda)

- Anti-fibrinolytic; available in Europe for many years- available in US (Lysteda) 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 or risk factors for VTE. Unknown if safe in conjunction with OCP.
- Side effects: Minimal

First Line Hormonal treatments

- First choice: Levonorgestrel IUD
  - >80% reduction in blood loss, decreased cramping, prevents/treats hyperplasia, highly effective birth control
  - Great option when want to avoid estrogen
  - Blood loss and satisfaction comparable to ablation, satisfaction comparable to hyst.
- 2nd choice: combined contraceptives (OCP, patch, ring) or DMPA
  - Proven to decrease irregular peri-menopausal bleeding (20 & 35 mcg);
  - Any type ok, 20 mcg preferred for women >40

Second Line Hormonal Options

- HRT (ie post-meno dosing):
  - More difficult to gain cycle control compared with OCP
  - Options with higher dose progestin may be more effective (FemHRT)
- Cyclic Progestins:
  - Less effective than NSAID’s and Levo IUD.
  - 21 day therapy more effective than 10 day but poorly tolerated
Surgical Treatments

- 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 future 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 or OCP’s, DMPA)

If persists:
- get 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?

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%
Fibroid Symptoms

- **Bleeding:**
  - Usually normal or menorrhagia (heavy but regular)
  - Occasionally menometrorrhagia if submucous or intracavitary
- **Pressure Symptoms**
- **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 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 vag hyst
- 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

- 40% decrease in size, 75-90% improved bleeding
- Most studies have short term follow-up only (5 yrs max). Will they re-grow? In 5yr f/u of RCT, 25% had hysterectomy
- Not recommended for women who want future fertility
- 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 by hemocue=9

Acute menorrhagia treatment

ABC's and Stop the bleeding!
- 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
- Transfusion prn
- If not effective, consider D&C, Foley bulb tamponade, emergency hyst
- Small RCT suggests high dose provera may be effective as well, 20mg tid

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 ocp’s X 4 days, 3 ocps x 4 days, 2 ocp X 4days then 1 ocp per day for 1-2 months (66-96 pills required).
- Must instruct no placebos and give at least 3 packs of pills at once.
What about too little bleeding?

Seven questions in evaluation of 2° amenorrhea
1. Pregnant?
2. Excessive hair growth or acne?  \( \rightarrow \) PCOS
3. Overweight?  \( \rightarrow \) Obesity induced anovulation
4. Breast secretions?  \( \rightarrow \) Hyperprolactinemia
5. Very thin, over-exercise, stress?  \( \rightarrow \) Functional hypothalamic amenorrhea
6. Hot flashes?  \( \rightarrow \) Premature ovarian failure
7. Pregnant recently complicated with infection or uterine surgery (D&C)?  \( \rightarrow \) 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 cliteromegaly: testosterone. If family history hirsutism or onset at puberty: 17 OHP

Role of progestin challenge test

- **Progestin challenge test** (10 mg Provera x 10 days) determines if 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)  \( \rightarrow \) combined contraceptives, dpaa, Mirena
2. **Obesity induced anovulation**  \( \rightarrow \) same
3. **Hyperprolactinemia** due to microadenoma  \( \rightarrow \) OCP’s or nothing, Bromocriptine if desires pregnancy or Sx bothersome
4. **Functional hypothalamic amenorrhea**-- protect the bones! (from lack of E2)  \( \rightarrow \) estrogen containing contraceptives
5. **Premature ovarian failure**  \( \rightarrow \) same
6. **Asherman’s syndrome**  \( \rightarrow \) Hysteroscopy
Patient #4

A 45 yo G1P0S1 presents with irregular menses. She has had irregular menses off and on for 2 years with occasional hot flashes. More recently, she has had nearly daily light bleeding and cramping for almost 2 months straight. She has a long history of infertility, had laparoscopic adhesiolysis many years ago and had a hysterosalpingogram that showed non-patent tubes.

Most likely diagnosis? Anovulatory bleeding
Must first rule out.....? Pregnancy

First trimester bleeding

- Occurs in 20 to 40% of pregnancies
- Up to ½ end in spontaneous abortion or ectopic
- **Ectopic Pregnancy** (2% of pregnancies):
  - Incidence has increased but death rate decreased due to early diagnosis and treatment. Nonetheless:
    - Leading cause of 1st trimester maternal death (6% of all maternal deaths in US)
    - Disparity: Deaths more likely in AA
  - 2/3 of women dying of EP had recently seen a clinician but had incorrect or delayed diagnosis

Ectopic Pregnancy

**GOAL: Early Diagnosis**

- Decreased chance of rupture (rupture can occur at any level of beta HCG and whether rising, falling or plateauing)
- Rupture associated with decreased fertility, increased morbidity and mortality
- More treatment options (eg methotrexate, conservative surgical treatment) if diagnose earlier
- Methotrexate more likely to be effective if diagnose earlier
Ectopic Diagnosis: Simplified

Patient pregnant & bleeding or pain:
1. Where is the pregnancy? → U/S (same day)
2. If we can’t tell where it is, is it normal or abnormal? → serial quantitative Beta-HCG
   - If Beta above threshold and no IUP = Abnormal
   - If Beta drops or rises very little = Abnormal
3. Once pregnancy determined to be abnormal or if undesired → uterine aspiration to determine if IUP. Ectopic treatment if not.

Back to the patient:
- Pregnancy is strongly desired
- Office U/S: No IUP is seen (thin endometrial stripe with fluid collection, could be early gestational sac). No adnexal masses. Trace free fluid.
- Beta-HCG=4000
- Rh- → Rhogam given (always give for any amount of first tri bleeding. Can give mini-dose if available)

No adnexal masses, no IUP
- Given no adnexal masses, does that rule out ectopic?
- Given no IUP, does that rule out normal pregnancy?

Role of ultrasound in ectopic diagnosis
- Only 2% of u/s are diagnostic for EP
  - “diagnostic” = Gestational Sac with yolk sac or fetal pole visualized outside uterus
- Normal adnexal exam does not exclude ectopic
- Suggestive of ectopic
  - Empty uterus + hCG above discriminatory zone (86% are EP)
  - Complex mass + fluid in cul-de-sac (94% are EP)

Main role of U/S is to rule in IUP
Ectopic Treatment: MTX vs surgery
- If hemodynamically unstable ➔ straight to OR
- If hemodynamically stable, depending on patient characteristics, choice of MTX vs surgery
  - No difference in future IUP rate (both groups decreased)
  - No difference in future ectopic rate (10-15%)
- MTX:
  - Less effective than salpingostomy (OR=0.38).
  - Efficacy related to b-hcg level (ranges from 98% for beta<1000 to 68% at >15,000)
  - 15% require a second dose
  - 5% have rupture despite MTX
  - Requires pt compliance and follow-up

Spontaneous Abortion & Early Pregnancy Failure
- 15-20% of clinically recognized pregnancies end in miscarriage
- 600,000-800,000 annually
- 1 in 4 women experience EPF in lifetime
- Early Pregnancy Failure replaces “missed abortion” and “blighted ovum” (terms from a pre-U/s era)
- Includes: anembryonic gestation and embryonic demise

Early Pregnancy Failure: Counseling
- Women blame themselves (“was it the stress?”)
- Wonder if it will happen again
Patient counseling should include:
- How common it is (encourage to talk to friends)
- Reassurance that it is beyond her control and unlikely to recur. (“Nothing could have been done to prevent it.”)
- Acknowledge/validate grieving
- No need to wait to attempt another pregnancy. Ok to try after resumption of menses (when emotionally ready)

Reference: Helping your patient to choose treatment for EPF
- Expectant: 66% at 2wks (higher if incomplete ab)
  - Advantages: Privacy, some can avoid surg trtment, ? Decr infx
  - Disadvantages: up to 6 wks to complete, more bleeding & more visits, less patient satisfaction
- Misoprostol (800 PV): 80% (higher if incomplete ab)
  - Advantages: Privacy, availability, most can avoid surgical trtment, ? Decr infx, similar satisfaction as surgical
  - Disadvantages: multiple visits, 30% require 2nd dose, more pain, N/V & bleeding than surgical
- Surgical Aspiration: 97-100%
  - Advantages: 2-4 hrs, high success rate, less blding & pain
  - Disadvantages: less available, rare surgical complications, ? Inc infx
Conclusions: Non-pregnant AUB

- **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
- **Persistent abnormal bleeding requires continued work-up even if EMB and/or ultrasound are negative**

Conclusions: Pregnant and bleeding

- **Maintain high index of suspicion for ectopic until IUP is definitively ruled in. Diagnose as quickly as possible to avoid rupture.**
- **2 step ectopic diagnostic process:** Where is the pregnancy (U/S), If can’t see the pregnancy, is it normal or abnormal (serial B-HCG).
- **Methotrexate is not for everyone, is associated with 5% rupture and may not improve future fertility**
- **SAB and early pregnancy failure very difficult for women—repetitive reassurance is necessary**