Evaluation & Management of Overactive Bladder

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Disclosures/Conflict of Interest/Bias

• I have no financial relationship with any of the companies that produce the products I’m about to discuss

• I have no conflicts of interest.

• I specifically don’t encourage OR discourage use of any particular product

Outline

• What type of female urinary incontinence (UI)?
  - Epidemiologic encouragement
  - Overactive Bladder (OAB) vs. Stress Urinary Incontinence (SUI)

• Classic/Typical Patient presentations
  - Key points of non-surgical/medical management
    - Diagnosis/Further testing/Rx choices
    - New medication options
  - New referral options

• Brief Summary

Why should you care?
Definitions

- **Stress Urinary Incontinence (SUI):**
  - involuntary leakage on effort or exertion, or on sneezing or coughing

- **Overactive Bladder (OAB):**
  - Frequency - 8 or more voids in 24 hours, <Q 3
  - Urgency - strong urgency & small volumes
  - Nocturia - ≥2 per night

- **Urge Urinary Incontinence (UUI):**
  - involuntary leakage accompanied by or immediately preceded by urgency

- **Mixed Incontinence: Both**

Jane

40-yo P3 who complains of leaking when she runs with her kids and plays tennis.
- "By then end of my game or run my pad is soaked"
- Started after my last child

Voids 1 times per night
2 cups of coffee daily
No medical problems
PE: "normal" pelvic although leaks a small amount with valsalva
- "weak" pelvic floor contraction
By description does Jane have:

1. Stress incontinence
2. Urge incontinence/OAB
3. Mixed incontinence

Differentiating OAB from SUI

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>OAB</th>
<th>SUI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urgency (strong, sudden desire to void)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Frequency with/without urgency (&lt;8 times/24 h)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Leaking during physical activity; eg, coughing, sneezing, lifting</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Amount of urinary leakage with each episode of incontinence</td>
<td>Large (if present)</td>
<td>Small</td>
</tr>
<tr>
<td>Ability to reach the toilet in time following an urge to void</td>
<td>Often no</td>
<td>Yes</td>
</tr>
<tr>
<td>Waking to pass urine at night</td>
<td>Usually</td>
<td>Seldom</td>
</tr>
</tbody>
</table>

Mary

35-yo healthy P1 bank executive who complains of:
   “going to the bathroom every hour”
   Can’t sit through a meeting, embarrassed, but can hold it if she has to

Voids 1 times per night
Drinks 5c of coffee per day
Med Hx: Anxiety
PE: 1/5 pelvic floor contraction
“small” cystocele
Does Mary need any of the following?

1. Post void residual
2. Urodynamics
3. Cystoscopy
4. UA/Urine Culture
5. All of the above

What is the necessary work-up for OAB?

- Post void residual
- Urodynamics
- Cystoscopy
- UA/Urine Culture

What would you offer Mary?

1. Behavioral Modification
   - Irritant reduction
   - Bladder retraining
2. Pelvic Floor Exercises
3. Medications
4. All of the above

3 Pillars of OAB 1st Line Management

- Behavioral Modification
  - Reduce Dietary Irritants, Control Intake, Bladder retraining

- Pelvic Floor Exercises - “Kegels”
  - Physical Therapy
    - E-Stim, Vaginal Cones (Plevnik)
    - Control the urge when it strikes

- Medications
Possible Dietary Irritants

**Emphasize Moderation Above Elimination**

- Alcohol
- Apples
- Aspartame
- Carbonated beverages
- Citrus Fruit/ Juices
- Chocolate
- Coffee (caf or decaf)
- Cranberries (+ juice)
- Grapes
- Guava
- Pineapple
- Strawberries
- Sugar
- Spicy Foods
- Tea (Black & Green - Not herbal)
- Tomato-based Foods
- Vitamin B
- Vinegar

Another good option for Mary

**Bladder Re-Training**

- **Goal**: Break cycle of frequency, urgency
  - Void every 3” on average
- **Process**: Gradually increase time between voids
  - Goal: Void every 3 hours
  - Identify shortest interval btw. voids
  - Void only after interval passes
  - Increase interval by 15-30 minutes weekly
- **RCT’s**: 50-80% success
- Works best if bother NOT leaking

Carol

74-ye P3 complains of soaking through her pads
- “Can’t reach toilet when I get the urge”
- Has been a problem for “years”

Voids 3 times per night
Drinks 4 cups of coffee per day
Med Hx: Htn
PE: “Moderate” cystocele & “weak” pelvic floor contraction
Quick side note

Which drug would you offer Carol 1st?

1. Tolterodine (Detrol)
2. Oxybutynin (Ditropan/Generic)
3. Darifenacin (Enablex)
4. Solifenacin (Vesicare)
5. Trespium (Sanıntıa)
6. Onabotulinumtoxin A (Botox)

Comparable efficacy

- Some women respond to one but not another
  - Try 2-3 before determining they aren’t helpful
  - Use for a minimum of a month
- Long acting drugs have fewer side-effects
  - Quotable Stats: 20-30% overall
    - Dry mouth/eyes: 20-30%
    - Constipation: 6-8%
    - Headache: 5-6%
- Newer drugs allow advancement of dosing by doubling pill
  - Darifenacin (Enablex): 7.5mg – 15mg
  - Fesoterodine (Toviaz): 4mg – 8mg
- Generics MUCH cheaper

Why treat with anti-muscarinics?

- Reduce leakage episodes
- Reduce the number of voids in 24h
- Increase maximum cystometric volume
- Increase volume at first contraction
- Increase residual volumes
- They DO NOT increase warning time to void
- They rarely cure but frequently IMPROVE a patient’s symptoms
Anti-cholinergics For OAB

<table>
<thead>
<tr>
<th>Drug</th>
<th>IR</th>
<th>BID/QD</th>
<th>LA/OQD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolterodine (Detrol)</td>
<td>1-2 mg</td>
<td></td>
<td>2-4 mg</td>
</tr>
<tr>
<td>Trospium (Sanctura)</td>
<td>20 mg</td>
<td></td>
<td>60 mg</td>
</tr>
<tr>
<td>Oxybutynin Chloride (Ditropan)</td>
<td>5 mg BID - TID</td>
<td>3.9 mg QD (OTC)</td>
<td>5/15 mg QD</td>
</tr>
<tr>
<td>Darifenacin (Enablex)</td>
<td>7.5/15 mg QD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solifenacin (Vesicare)</td>
<td>5/10 mg QD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fesoterodine (Toviaz)</td>
<td>4/8 mg QD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Contraindications
- Glaucoma
- Narrow angle
- Bowel obstruction
- Kidney/Hepatic Dz.

Side effects
- Dry mouth
- Constipation
- Blurred vision
- Headache
- CNS effects

Generics
- Oxybutynin
- Tolterodine

Contraindications
- Glaucoma
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- Dry mouth
- Constipation
- Blurred vision
- Headache
- CNS effects

Generics
- Oxybutynin
- Tolterodine

Alice

83-ya who complains of frequent urination when she is “out and about”
- 1st complaint: Goes too often @ church
- Not bothered @ home or @ night
- NO dietary irritants except 1g tea
- Med Hx: Htn, Glaucoma (Narrow)
- PE: Pelvic floor strength is poor
- Significant atrophy (PMP since 50)

Which drug would you offer Alice?

1. Oxybutynin (Ditropan/Generic)
2. Darifenacin (Enablex)
3. Solifenacin (Vesicare)
4. Transvaginal Estrogen
5. Trospium (Sanctura)
6. Onabotulinumtoxin A (Botox)
Anti-cholinergics For OAB

<table>
<thead>
<tr>
<th>Drug</th>
<th>IR</th>
<th>LA</th>
<th>XR</th>
<th>OTC</th>
<th>ER</th>
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<tbody>
<tr>
<td>Tolterodine (Detrol)</td>
<td>1</td>
<td>2</td>
<td>2-4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Trospium (Sanctura)</td>
<td>20</td>
<td>60</td>
<td>60</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Oxybutynin Chloride (Ditropan)</td>
<td>5</td>
<td>3.9</td>
<td>5/10</td>
<td>0.9</td>
<td>5/10/15</td>
</tr>
<tr>
<td>Darifenacin (Enablex)</td>
<td>7.5/15</td>
<td>5</td>
<td>5</td>
<td>5/10/15</td>
<td>5/10/15</td>
</tr>
<tr>
<td>Solifenacin (Vesicare)</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5/10</td>
<td>5/10/15</td>
</tr>
<tr>
<td>Fesoterodine (Toviaz)</td>
<td>4</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

- **Contraindications**
  - Glaucoma
  - Narrow angle
  - Bowel obstruction
  - Kidney/Hepatic Dz.

- **Side effects**
  - Dry mouth, Constipation, Blurred vision, Headache, CNS effects

- **Dates of Release in US**
  - 1999: Ditropan ER
  - 2001: Detrol LA
  - 2004: Sanctura
  - 2005: Enablex
  - 2005: Vesicare
  - 2008: Toviaz

Estrogen & OAB

- **Women on combined E/P are more likely to experience the onset of incontinence or worsening of symptom**
- **Mechanism unknown**

Carol returns 3 years later

Now a 77-yo who complains of worsening UUI
- "Soaking myself 2-3 times a week"
- Leakage just happens with no warning

PT: Can't improve her pelvic contraction any more
Eliminated all irritants

DOESN'T want surgery

Consider
- Mirabegron (Myrbetriq - Astellas)
  - β3 agonist
  - FDA approved for OAB July 2012
  - First new class of drug for OAB in 30yrs
  - 50 or 100mg Daily best studied
  - Significantly better than placebo, but NOT better than Tolterodine
- **AEs**
  - Dry Mouth: 3%
  - ?Hypertension/Heart rate
June

68-yo P3 who complains frequent urination
- “I'm going to the bathroom every hour”
- “Can't sleep because my bladder wakes me up”

Voids 4 times per night
Drinks 2 cups of coffee per day
Med Hx: Anxiety

ROS: insomnia; loss of appetite; doesn’t feel like leaving house since cat died

What are the options for June?

---

Ann

60-yo P1 who says she urinates 15X/day and 3X per night

“Can't resist the urge when I get it”
“I'm constantly leaking”

Had surgery for SUI 2 yrs ago

NO dietary irritants
Med Hx: Htn
PE: Kegel 4/5

Does Ann need any of the following?

1. Post void residual
2. Urodynamics
3. Cystoscopy
4. UA/Urine Culture
5. All of the above
When to consider additional work-up?

- Post void residual/Urodynamics
  - Neurologic issue - CVA, DM, back surgery
  - History of prior pelvic reconstructive or radical surgery
    - Slings in particular
- Cystoscopy
  - Hematuria
  - Long history of smoking
  - History of stone disease
  - Recurrent UTI

3 Options for 2nd Line Management

- Bladder Botox injections (Allergan)
- Neurostimulation
  - Interstim (Medtronic)
  - Posterior Tibial Nerve Stimulation (PTNS)

Review of Key Points

- Work-up
  - History alone typically sufficient
    - Nocturia: triggers; can’t reach the bathroom
    - Retention is unlikely unless bladder can’t squeeze or urethra tight
- Management
  - Irritants/behavior, PFEs & Meds
  - Pelvic PT better than self-directed PFE
  - Try 2-3 meds: Take advantage of newer dosing options; New Med
  - Use PRN immediate release if circumstances appropriate
    - Nortes (Promiben)
  - Vaginal estrogen effective in atrophic PMP women
- If unimproved/symptom confusion:
  - Diary
  - Consider Depression/other meds
- If nothing works consider referral
  - Neuromodulation or Botex

OAB Management Overview
RECURRENT URINARY TRACT INFECTIONS

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University of Washington
Division of Urogynecology
Department of Obstetrics and Gynecology
March 27, 2015

OBJECTIVES

• Definition/Epidemiology
• Approach to premenopausal and postmenopausal women
• A couple tricky cases

Definitions

• UTI
  ≥100,000 CFU/ml and symptom (CDC)

• Recurrent UTI
  ≥3 UTIs in one year
  ≥2 UTIs in 6 months

DISCLOSURES

• No financial relationships to disclose.
Epidemiology

- >50% of women have at least 1 UTI
- 3-5% of women have recurrent UTIs

A 25-year-old woman presents with 3 UTIs in the last year. She is sexually active with one male partner and has no other past medical or surgical history. Currently asymptomatic. What is your next step?

- A. Renal ultrasound
- B. Urinalysis and urine culture
- C. Postcoital voiding
- D. Postcoital antibiotics
- E. Postcoital douching
- F. Change birth control to diaphragm and spermicide

Why is she having rUTIs?

- Sex
  - Bacteria from vagina and rectum->urethra->bladder
- Other risk factors:
  - Prior UTI
  - Spermicides
  - Family history UTI
  - Diabetes, obesity, catheterization
  - Congenital anomalies

Evaluation

- No imaging
  - Uncomplicated UTI
- No urine culture
  - Not symptomatic
  - Don’t screen for bacteriuria – no need to treat (unless pregnant or planning urologic surgery)
Prevention

• Things that don't help:
  • Douching
  • Postcoital voiding
  • Spermicides
    (increase risk)
  • Drinking more water

Prevention

• Cranberries?
  • Good in theory: proanthocyanidins inhibit attachment of uropathogens to urothelium
  • Mixed evidence
  • Why not?
    • Money
    • Calories
    • Sugar

Prevention

• Antibiotics?
  • Yes!
  • Postcoital (peri-coital)
  • 92% effective
    • Nitrofurantoin 50-100mg PO daily prn
    • Trimethoprim 100mg
    • TMP-SMX 40/200mg or 80/400mg
    • Cephalexin 250mg

### Post-coital antimicrobial prophylaxis regimens for women with recurrent urinary tract infection

<table>
<thead>
<tr>
<th>Regimens</th>
<th>Expected UTIs per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethoprim-sulfamethoxazole 40 mg/200 mg</td>
<td>0.20</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole 80 mg/400 mg</td>
<td>0.00</td>
</tr>
<tr>
<td>Nitrofurantoin 50 mg or 100 mg</td>
<td>0.10</td>
</tr>
<tr>
<td>Cephalexin 250 mg</td>
<td>0.03</td>
</tr>
<tr>
<td>Norfloxacin 125 mg</td>
<td>0.00</td>
</tr>
<tr>
<td>Doxycycline 100 mg</td>
<td>0.06</td>
</tr>
</tbody>
</table>
Summary: Sexually active young women with recurrent UTIs -> postcoital antibiotics

- Let her off the hook
  - It is okay to fall asleep after sex
  - She is not wiping wrong
  - She doesn't need to drink so much water she has to get up all night to pee

Goal: No UTIs for 6-12 months, then re-assess

A 55-year-old woman presents with 3 UTIs in the last year. She had a couple UTIs in her early 20s and has no other past medical or surgical history. Currently asymptomatic. What is your next step?

- A. Renal ultrasound
- B. Urinalysis and urine culture
- C. Vaginal estrogen
- D. Oral estrogen
- E. Postcoital antibiotics

Why is she having rUTIs?

- Menopause.
- Other risk factors:
  - Prior UTI
  - Prolapse
  - Incomplete bladder emptying

Why is she having rUTIs?

- Menopause.
- Falling estrogen levels -> Changes in vaginal epithelium -> Lactobacilli fail to thrive -> Vaginal pH rises to 7 -> E.coli and other harmful bacteria colonize vagina -> Ascending bladder infections
Evaluation

- No need for imaging
- Uncomplicated UTI
- No need for urine culture
  - Not symptomatic, so don’t screen

Prevention

- Things that don’t help:
  - Douching
  - Postcoital voiding
  - Drinking more water
  - Oral estrogen/HRT

Prevention

- Vaginal estrogen
  - Treat vaginal atrophy
  - Repopulate the vagina with lactobacillus
  - Reduce colonization of harmful bacteria
  - Note: Warn her about the warnings!
  - Same as oral HRT but low systemic absorption, so only small, theoretical risk

Prevention

Vaginal estrogen
- Estradiol 0.1mg/gm cream (Estrace)
  - 0.5g 2 nights per week
- Estrogen 0.625mg/gm cream (Premarin)
  - 0.5g 2 nights per week
- Estradiol 10mcg tablets (Vagifem)
  - one tab 2 nights per week
- Estradiol 2mg ring
  - one ring every 3 months
  (throw away the applicators)
**Prevention**

- Prophylactic antibiotics
  - Can reduce UTIs up to 95%
  - Side effects
  - Antibiotic resistant organisms
- TMP-SMX 40/200 or 80/400 nightly
- Nitrofurantoin 50-100mg nightly
- Cephalexin 125-250mg nightly
- TMP 100mg nightly
- Fosfomycin 3g every 10 days

Goal: 6 months no UTIs
### Prevention

- **Probiotics** – some evidence  
  - Nightly x 5 nights then weekly x 10 weeks  
  - Works with vaginal estrogen?  
  - $\$\$  
  - ?Stability  
- **Methenamine hippurate** – limited evidence  
  - PLUS Vitamin C (acidifies urine)  
  - -> formaldehyde  
  - Reduces UTIs 6mo  
  - ? Long term

### Prevention

- **Cranberry** – maybe, mixed data  
- **D-mannose** – maybe, no good data

### Plan

- Send cultures  
  - When symptomatic  
  - Prior to abx (empiric or self-treatment OK)  
  - Sensitivity to guide abx (preferable)  
  - Determine need for additional work-up  
    - Eg. proteus, relapsing, etc  
    - Cystoscopy, CT non-contrast

### Treat acute UTIs

- **Empiric antibiotics reasonable**  
  - Nitrofurantoin monohydrate/macrocrystals (100 mg twice daily for 5 days)  
    - + minimal resistance  
    - + propensity for collateral damage.  
    - + Efficacy 84-95%  
    - +/- need GFR >60  
  - Trimethoprim-sulfamethoxazole (160/800 mg twice-daily for 3 days)  
    - + Efficacy 90-100%  
    - Not if local resistance rates of uropathogens > 20%
Empiric antibiotics continued
- Fosfomycin (3g single dose)
  + easy, safe
  + Efficacy 91%
- Fluoroquinolones efficacious in 3-day regimens
  - side effects
  + Efficacy 85-98%
  - should be reserved for important uses other than acute cystitis

Treat acute UTIs

Or wait for sensitivities
- +/- symptoms last 37% longer but no increase in pyelonephritis
  + good antibiotic stewardship

Summary: Postmenopausal woman with recurrent UTIs -> vaginal estrogen
- Minimal systemic absorption
- Decreases irritation
- Decreases dyspareunia

A 30-year-old woman presents with 6 “UTIs” in the last year. She was treated empirically, and review of her labs show two normal UA’s and no urine cultures at all. She is sexually active with one male partner and has no other past medical or surgical history. Currently symptomatic. What is your next step?
- A. Renal ultrasound
- B. Urinalysis and urine culture
- C. Cystoscopy
- D. CT without contrast
IC?

• Interstitial cystitis/painful bladder syndrome
• Many episodes of UTI symptoms but no positive cultures
• Diagnosis of exclusion
• Keep it in mind

A 65-year-old woman presents with 6 UTIs in the last year despite vaginal estrogen, cranberry pills, methenamine, Vitamin C, lactobacillus, trimethoprim. She is worried because she never feels like a UTI, but her doctor tells her she has one almost every time they check. Lab review confirms urine cultures with >100,000 CFU/ml bacteria.
What should you do next?
• A. Stop sending urine cultures
• B. Change from trimethoprim to nitrofurantoin
• C. Add nitrofurantoin
• D. Cystoscopy

Asymptomatic bacteruria

• Unless she is pregnant or planning a urologic procedure, we don’t want to know.

A 65-year-old woman presents with 4 UTIs in the last year despite vaginal estrogen, cranberry pills, and methenamine. Which of the following is the least good prophylactic antibiotic?

• A. Ciprofloxacin 250mg nightly
• B. Nitrofurantoin 50mg nightly
• C. Trimethoprim 100mg nightly
• D. Cephalexin 250mg nightly
• E. Fosfomycin 3g every 10 days
• F. TMP-SMX 40/200 nightly
Fluoroquinolones

- Save them for more dangerous infections when possible

Thank you
Chronic Pain: Non-Opiate Medications in the Complex Patient

March 27, 2015

Women's Health Care Update
University of Washington

Sharon K. Gill, M.D.
Director, Women's Health Program, VA Puget Sound
Clinical Instructor, University of Washington

Disclosures

- No financial disclosures
- Will discuss many off-label uses of medications
- Evidence for effectiveness of non-opiate medications is limited
- Sources, if not otherwise specified:
  - UpToDate: Review articles, Drug information
  - Micromedex
  - FDA website
  - Reprotox

Chronic Pain Mgt Overview

1) Underlying pain source evaluation
   • Hx, PE, labs, imaging, specialty referral
   • STOP evaluation when done
2) Mental health treatment
3) Sleep
4) Activity, movement, PT, nutrition, weight
5) Medications
   • Non-opiate
   • Opiate
6) Counseling, coaching, close follow-up
Sources

- If not otherwise specified:
  - UpToDate
  - Review articles
  - Drug reference articles
  - MicroMedex
  - FDA website
  - Reprotox

Learning Objectives

- Be familiar with major risks and expected benefits of commonly used non-opiate pain medications
- Be comfortable tailoring non-opiate chronic pain medication recommendations to each patient’s co-morbidities and treatment preferences

Chronic Pain in Women

- Fibromyalgia
  - 3.4% of women vs. 0.5% of men
  - Concomitant depression, fatigue, insomnia
- Prevalence of painful musculoskeletal conditions increasing among young veterans and higher rates in women, congruent with general population

Medication Classes

- Non-steroidal anti-inflammatories (NSAID)
- Acetaminophen
- Tri-cyclic anti-depressants (TCA)
- Anti-epileptics (AEDs)
- Serotonin norepinephrine re-uptake inhibitors (SNRI)
- NOT opiates
- Adjunctive therapies
  - Anti-depressants
  - Sleep aids
**Major Challenges**

- Sedation
- Serotonin syndrome
- Medication interactions
- Concurrent mental health treatment
- Frequent dosing, complex titrations
- Weight gain
- Medication withdrawal

**Major Strengths**

- Beneficial secondary med effects
  - Sedation
  - Depression/anxiety treatment
  - Hot flashes
  - Migraine prophylaxis
- Old, familiar meds (some of them)
- Less risky than opiates
- Chronic med for chronic condition

**Co-morbidities that Vex**

- CVD (CAD/stroke)
- Prolonged QT
- Hypertension
- Bipolar
- Liver disease
- Kidney disease
- GERD/Peptic Ulcer Disease
- Obesity
- Fatigue
- Pregnancy

**Co-morbidities as Opportunities**

- Migraine
- Insomnia
- Depression/anxiety
- Incontinence
- IBS/diarrhea
- Hot flashes
- Alcohol abuse
**Case #1:** 47 y/o woman with CKD-3 (eGFR=45), cirrhosis, obesity, HTN, and depression comes to clinic asking for medication for chronic back pain. She also has insomnia, partly due to pain, but does not want to be drowsy during the workday. In addition to low-dose acetaminophen, which med would you recommend?

1. Pregabalin
2. Venlafaxine
3. Desipramine
4. Gabapentin
5. Amitriptyline

**Tricyclic Antidepressants (TCA)**
- High dose for depression (100-150mg)
- Low dose for pain (10-50mg)
- Major Risks / Adverse Effects:
  - Cardiac disease / hx stroke - contraindicated
  - Overdose
  - Bipolar – trigger mania
  - Dry mouth
  - Constipation
- Benefits:
  - Sleep
  - Mild anti-depressant effect at low dose
  - Incontinence
  - Migraine prophylaxis

**Tricyclics**
- Amitriptyline → nortriptyline
- Imipramine → desipramine

<table>
<thead>
<tr>
<th>TCA</th>
<th>Anticholinergic</th>
<th>Drowsiness</th>
<th>Weight Gain</th>
<th>Sexual Dysfunction</th>
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<tbody>
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<td>4+</td>
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<td>3+</td>
<td>3+</td>
<td>4+</td>
<td>3+</td>
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<tr>
<td>Desipramine</td>
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<td>4+</td>
<td>1+</td>
<td>unknown</td>
</tr>
</tbody>
</table>

Tricyclics

- Multiple small trials show at least some effectiveness for multiple types of chronic pain (not always robust studies)
  - Neuropathic
  - Fibromyalgia
  - Chronic low back pain
  - Headache
  - Osteoarthritis
- Number needed to treat ~2


Tricyclics

- Concentrations vary up to 10-fold among individuals taking same dose
- 5% pop’n poor metabolizers $\rightarrow$ ↑ drug concentration $\rightarrow$ ↑ adverse effect
- Poor metabolizers need ~30-50% of usual dose, check levels to avoid overdose


Case #2

- Ms. S is a 59 y/o woman with diabetes, hypothyroidism, HTN, migraine, fibromyalgia, PTSD, and chronic back pain who comes into clinic for a post-hospitalization visit. She reports that she was found by medics naked on the living room floor, sweating and confused. Her discharge diagnosis is TCA toxicity.
- Medication list:
  - Amitriptyline 200mg
  - Sertraline 200mg
  - Carisoprodol
  - Clonazepam
  - Cyclobenzaprine
  - Etodolac
  - Levothyroxine
  - Lisinopril
  - Metoclopramide
  - Methadone 15mg TID
  - Risperidone 2mg QHS
  - Zolmitriptan prn

**Case #2: What else is going on?**

1. Only TCA toxicity
2. Hyperthyroidism
3. Serotonin syndrome
4. Benzodiazepine withdrawal
5. Opiate withdrawal
Serotonin Syndrome

- Autonomic: hyperthermia, flushing, diaphoresis, dizziness, labile BP, tachycardia
- Nausea, vomiting, diarrhea
- Neuromuscular: Myoclonus, rigidity, tremor
- Mental status: agitation, delirium → coma
- Seizures
- Linezolid = MAOI → high risk of serotonin syndrome
- All anti-depressants may contribute
- Cyclobenzaprine, tramadol, anti-psychotics

Case #3: 56 y/o woman is a new patient in your clinic. She has CAD, CKD, cirrhosis, PTSD, bipolar, migraine, and fibromyalgia. She uses a fentanyl patch for her fibromyalgia, but she has heard that opiates are dangerous and would like to stop. She asks if there are any other medications to help her pain?
1. Nortriptyline – unsafe in heart disease and bipolar
2. Venlafaxine – unsafe in chronic liver disease
3. Gabapentin – OK
4. Duloxetine – unsafe in chronic liver disease
5. Pregabalin – also OK, but $$$

Drug Costs

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Cost per month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>1000mg TID</td>
<td>$4</td>
</tr>
<tr>
<td>Naproxen</td>
<td>440mg BID</td>
<td>$8</td>
</tr>
<tr>
<td>Desipramine</td>
<td>25mg QHS</td>
<td>$10</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>25mg QHS</td>
<td>$14</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>600mg TID</td>
<td>$23</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>150mg BID</td>
<td>$300</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>150mg BID</td>
<td>$40</td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>100mg BID</td>
<td>$250</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>60mg Daily</td>
<td>$50</td>
</tr>
<tr>
<td>Milnacipran</td>
<td>50mg BID</td>
<td>$126</td>
</tr>
</tbody>
</table>

Source: GoodRx.com, amazon.com
Gabapentin

- AED
- FDA-approved indications:
  - Partial seizures
  - Post-herpetic neuralgia
- Major Risks / Adverse Effects:
  - Sedation / loopy / unsteady gait
  - Myoclonus / tremor
  - Toxicity
- Benefits:
  - Sedation (higher bedtime dose)
  - Migraine prophylaxis
  - Hot flashes
  - Restless Leg Syndrome
  - Alcohol craving reduction


Gabapentin

- RCT: Double-blind placebo-controlled
- Population: n=75 in each group
- Duration: 12 weeks
- Intervention: Gabapentin 1200-2400mg/d
- Measure:
  - Brief Pain Inventory (0-10)
  - Response = 30% or more decrease
- Results:
  - Treatment group: 51% response
  - Placebo group: 31% response


Gabapentin - Administration

- Dose titration
  - Start 300mg QHS usually
  - 100mg QHS in med-sensitive patients
  - Titrate up by 300mg dose every 5 days
  - Maximum dose 3600mg/24hours
- Do not stop abruptly – risk of seizure
- Counseling and close/frequent follow-up crucial
  - If adverse effect, back to prior dose
  - If no effect at goal dose, need to continue increasing to maximum dose
  - Patients frequently stop medication at initial titration goal if not effective at that dose.

Gabapentin - Nuances

- Mood
  - Mood stabilizer in some patients
  - Suicidal ideation or action 1/500
- Adverse effects, uncommon
  - Myoclonus
  - Rhabdomyolysis
  - Allergy: rash, anaphylaxis, DRESS
  - Toxicity: caution if AKI or CKD
- Interactions
  - Few specific
  - Other CNS depressants
Pregabalin

- AED
- FDA Indications:
  - Neuropathic pain (DM, spinal cord injury, postherpetic)
  - Fibromyalgia
  - Partial seizure (adjunct)
- Major Risks / Adverse Effects:
  - Sedation / loopy / unsteady gait
  - Dizziness
  - Myoclonus / tremor
  - Renal dosing
  - Weight gain
- Benefits:
  - Sedation (higher bedtime dose)
  - Often better tolerated than gabapentin

Amitriptyline vs. pregabalin

- Design: RCT, open-label
- Population: Consecutive patients with chronic LBP seen by a neurology clinic in N. India; half with radiculopathy, half with localized back pain. N=200
- Outcome measures:
  - Visual analog pain scale
    - Response (treatment success) = 50% decreased pain score
    - Baseline = 6.7 on the 0-10 point scale
  - Oswestry Disability Index
    - Response (treatment success) = 20% decrease
    - Baseline = 40% (moderate to severe pain, limits work, sleep)
- Methods:
  - Randomized to amitriptyline or pregabalin for 14 weeks
  - Starting dose increased as needed to standard max dose


Amitriptyline vs. pregabalin: Results after 14 weeks:

- Ammitriptyline 10-50mg
  - 57% response pain score
  - Mean pain score 2.8 (b/l 6.7)
  - 65% response disability
  - Mean ODI score = 20%
  - 18 pts ADE (sedation, dry mouth)
  - Dose was not different in group with meaningful pain score response vs. group without response
  - Pain and disability responses not different between the localized vs. radicular pain subgroups.
  - Similar number lost to f/u (14 amitriptyline vs. 15 in pregabalin group)
  - Same number stopped medication due to significant adverse effect

  - Pregabalin 75-300mg bid
    - 39% response pain score
    - Mean pain score 3.8 (b/l 6.7)
    - 50% response disability
    - Mean ODI score = 25%
    - 21 pts ADE (sedation, vertigo)

- Case #4: 35 y/o woman comes to clinic requesting help for insomnia, fatigue, difficulty concentrating, and chronic pain due to fibromyalgia. Desipramine made her feel weird and tired; gabapentin caused sedation and weight gain. You prescribe venlafaxine 37.5mg bid with titration to 75mg bid. At one-month f/u visit, she reports depression and sleep have improved, but her fibromyalgia pain is no better. What would you do next?

  1. Increase venlafaxine dose
  2. Decrease venlafaxine dose
  3. Change to duloxetine
  4. Change to oxycodone
  5. Add nortriptyline
SNRIs: Serotonin > Norepinephrine Re-uptake Inhibitors (venlafaxine, duloxetine)

- FDA Indications:
  - Venlafaxine: MDD, GAD, panic, social phobia
  - Duloxetine: MDD, GAD, fibromyalgia, diabetic peripheral neuropathy, chronic MSK pain
- Major Risks:
  - GI symptoms at initiation
  - Increased BP (venlafaxine)
  - Withdrawing symptoms
  - Hepatotoxicity, elevated liver enzymes: avoid if chronic liver disease or alcohol abuse.
- Benefits:
  - No weight gain
  - Non-drowsy (venlafaxine sometimes mildly sedating)
  - Works on both depression and pain (high-dose venlafaxine)

Milnacipran = SNRI

- Norepinephrine > serotonin reuptake inhibitor
- FDA indicated for Fibromyalgia
- Major Risks:
  - Increased BP and HR; caution in cardiac patients
  - Serotonin syndrome
  - Hepatotoxicity (avoid if alcohol abuse or liver disease)
  - GI symptoms common (nausea, constipation)
- Benefits:
  - No sexual dysfunction
  - No weight gain
  - No insomnia/agitation
  - Anticholinergic effect mild (=desipramine)

Case #5: Ms. H is a 52 y/o woman with hepatitis C, lupus, osteoarthritis of both knees and back, fibromyalgia, HTN, PTSD, bipolar disorder, and active polysubstance abuse (heroin and methamphetamine). She has failed to follow-up with rheumatology, addiction treatment, and hepatology. She is at the front desk without an appointment loudly requesting oxycodone now. How can you best help her chronic pain?

1. Prescribe oxycodone
2. Prescribe gabapentin
3. Walk her to the addictions treatment clinic
4. Ask RN to call her monthly to help arrange specialty clinic visits and offer support
5. Mindfulness-based stress reduction for yourself and clinic staff

Polypharmacy – in a good way

- Medications from different classes
- Synergy: nortriptyline + gabapentin better than either alone- neuropathic pain
- Gabapentin + SNRI = OK
- Pregabalin + SNRI = OK
- TCA + duloxetine \(\rightarrow\) incr TCA levels
- TCA + venlafaxine \(\rightarrow\) QT prolongation

NSAIDs
- Anti-inflammatory
- Not effective for fibromyalgia
- Major risks:
  - GI Bleeding
  - Kidney Injury
  - Hypertension
  - Cirrhosis
- Benefits
  - Non-sedating
  - Not serotonergic
  - Inexpensive/OTC

Acetaminophen
- First-line for Osteoarthritis, LBP
- No effect on inflammation
- Major Risks:
  - Overdose (e.g. OTC cold remedies)
  - Liver disease
  - Concomitant alcohol
- Benefits:
  - Gentle for GI tract
  - No renal toxicity
  - No anti-platelet effect
  - Inexpensive/OTC

Acetaminophen
- Maximum dose
  - 1000mg Q6hours
  - 3000mg in 24 hours
- OK to use up to 2000mg / 24 hours in hepatitis C patients
- No more than 2000mg / 24 hours if alcohol use
- Safe in pregnancy

Tramadol
- Opiate + norepinephrine and serotonin reuptake inhibitor
- Major Risks:
  - NNT ≈ NNH
  - Interacts with anti-depressants, risk of serotonin syndrome
- Benefits:
  - short-term effectiveness
Non-opiate Med Summary

<table>
<thead>
<tr>
<th>Med</th>
<th>Start</th>
<th>Max</th>
<th>Pros</th>
<th>Cons</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tylenol</td>
<td>Any</td>
<td>1000mg/dose, 3000mg/day</td>
<td>No</td>
<td>GI upset, non-sedating</td>
<td>Liver toxicity with overdose</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Any</td>
<td>Naproxen: 500mg bid</td>
<td>Ibuprofen: 800mg tid</td>
<td>Non-sedating</td>
<td>Kidney and GI risk, unsafe in cardiac disease.</td>
</tr>
<tr>
<td>TCAs</td>
<td>10mg qhs</td>
<td>Usually 50mg for chronic pain. Up to 100-150mg for depression.</td>
<td>Helps sleep, avoid weight gain.</td>
<td>Dry mouth, constipation, sedation.</td>
<td>Unsafe if CVD/CVA. Serotonin syndrome.</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>300mg daily (100mg if very med-sensitive)</td>
<td>1200mg tid</td>
<td>Helps sleep, avoid weight gain.</td>
<td>Sedation, dizziness, weight gain.</td>
<td>Oldie/goodie. Does not interact with MH meds, generally a mood stabilizer.</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>37.5mg bid</td>
<td>225mg/day (75mg tid)</td>
<td>No weight gain. Works directly for pain, as well as depression treatment.</td>
<td>GI sx's at start. Incr BP.</td>
<td>Withdrawal sx's, taper over several weeks.</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>30mg daily x one week</td>
<td>60mg daily (up to 120mg for depression)</td>
<td>Also treats depression, no weight gain, no sedation.</td>
<td>GI sx's at initiation (less than venlafaxine). Withdrawal sx's.</td>
<td>Expensive</td>
</tr>
<tr>
<td>Milnacipran</td>
<td>12.5mg daily x 1d</td>
<td>25mg bid x 4d</td>
<td>Usual: 50mg bid Max: 100mg bid</td>
<td>Renal disease: reduce by 50% if CrCl &lt;30</td>
<td>Expensive</td>
</tr>
<tr>
<td>Tramadol</td>
<td>50-100mg q4-6hrs</td>
<td>400mg/day</td>
<td>Not usually sedating, better tolerated than opiates, less addiction (but still potential).</td>
<td>Increased risk of suicide, and risk of serotonin syndrome if on other serotonergics.</td>
<td>Acts like opiate, inhibits serotonin and norepinephrine uptake.</td>
</tr>
</tbody>
</table>

Co-morbidities that Vex… Less

- CVD (CAD/stroke): no TCA
- Prolonged QT: no TCA
- Hypertension: no NSAID, +/- venlafaxine
- Bipolar: no TCA, +psychiatry collaboration
- Liver disease: no SNRI
- Kidney disease: no NSAID, caution gaba/pregab
- GERD/PUD: no NSAID, nausea SNRI
- Obesity: avoid gabapentin, pregabalin, +/- TCA
- Fatigue: avoid gabapentin, pregabalin, +/- TCA
- Pregnancy: avoid all if possible

NSAIDs - selected nuances

- Theoretically effectiveness similar, but individual effectiveness is idiosyncratic.
- Naproxen lowest CVD risk
- Salsalate, meloxicam lower GI bleed risk
- Interact with:
  - Aspirin and warfarin: increases bleeding risk
  - Lithium: increases kidney toxicity
  - SSRIs: increases bleeding risk
  - Venlafaxine, duloxetine, and milnacipran: increases bleeding risk
  - ACEI/ARB: increases kidney toxicity, decreases anti-hypertensive effect of ACEI
  - CCB: increases GI bleeding risk, decreases anti-hypertensive effect of CCB
Evidence comparing non-opiates

- Efficacy similar


Case GT

- Ms. T is a 57 y/o woman with lupus, fibromyalgia, migraine, diabetes, and migraine presented two months ago to clinic requesting help with pain. You started her on gabapentin titration 300mg qhs → 600mg tid. You talked to her on the phone 3 weeks ago and she was pleased with the pain relief and migraine reduction effect of gabapentin. Today, you receive a call that she was admitted to the hospital...

Case GT

- Four days prior to admission, she developed nausea, vomiting, and diarrhea. Her granddaughter and daughter had similar symptoms the week prior. On the day of admission, she awoke feeling weak and dizzy.

Gabapentin

- Pharmacology:
  - Structurally similar to GABA
  - Does not bind/block GABA or its receptors, nor does it affect uptake/degradation of GABA
- Mechanism of Action: unknown
Gabapentin Toxicity

- Toxic Dose: 40-100g in healthy adult
- Mild-moderate
  - Sedation
  - Ataxia
  - Slurred speech
  - Nystagmus
  - GI upset
- Severe
  - Hypotension
  - CNS depression requiring intubation
- Treatment
  - No reversal agent or antidote
  - Time: several hours, up to days if kidney failure
  - BP and airway support if needed
  - Can be removed by hemodialysis
Medical Management Of Early Pregnancy Loss: Everyone Can Do It

Sarah Prager, MD, MAS
Department of Obstetrics and Gynecology
University of Washington
Women's Health Update

Objectives
- Discuss Definitions of Early Pregnancy loss (EPL)
- Review Etiology of EPL
- Review Diagnosis of EPL
- Describe evidence-based medical management of EPL

Disclosure
- I train providers in Nexplanon insertion and removal
- I do not receive any honoraria for this

Nomenclature
- Early Pregnancy Loss/Failure (EPL/EPF)
- Spontaneous Abortion (SAb)
- Miscarriage

These are all used interchangeably!
Early Pregnancy Loss is becoming the preferred term
Terminology

• MISSED ABORTION: a non-viable pregnancy that has been retained in the uterus without spontaneous passage for at least 4 weeks since the demise.

• EARLY PREGNANCY LOSS: any abnormal intrauterine first trimester pregnancy

---

EPL Definitions

<table>
<thead>
<tr>
<th>TERM</th>
<th>EXPLANATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Abortion</td>
<td>All pregnancy tissue has passed from uterus</td>
</tr>
<tr>
<td>Incomplete Abortion</td>
<td>Some pregnancy tissue remains in uterus</td>
</tr>
<tr>
<td>Inevitable Abortion</td>
<td>Cervix is open so pregnancy is going to pass</td>
</tr>
<tr>
<td>Threatened Abortion</td>
<td>Bleeding during pregnancy with closed cervix and pregnancy appears viable</td>
</tr>
<tr>
<td>Anembryonic Gestation</td>
<td>Gestational sac with mean sac diameter ≥16 mm transvaginally without embryo</td>
</tr>
<tr>
<td></td>
<td>Gestational sac does not grow over ≥5 days</td>
</tr>
<tr>
<td>Embryonic Demise</td>
<td>Embryo present, &gt;5mm long and no gestational cardiac activity</td>
</tr>
<tr>
<td>Fetal Demise</td>
<td>Fetus present with no gestational cardiac activity</td>
</tr>
</tbody>
</table>

---

Background

• Early Pregnancy Loss is the most common complication of early pregnancy
  • 8–20% clinically recognized pregnancies
  • 13–26% all pregnancies
  • ~800,000 EPL each year in the US
  • 80% of EPL occur in 1st trimester

---

Imperfect obstetrics: most don’t continue

Samantha

- 26 yo G2P1 presents to your office for a new ob visit. An ultrasound shows a CRL of 7mm but no cardiac activity.
- She wants to know why this happened.

The most likely reason for her EPL is:
1. Chromosomal abnormality
2. Maternal smoking
3. Paternal marijuana use
4. Maternal alcohol use
5. Too much maternal exercise

Etiology

- 33% anembryonic
- 50% due to chromosomal abnormalities
  - Autosomal trisomies 52%
  - Monosomy X 19%
  - Polyploidies 22%
  - Other 7%
- Host factors
  - Structural abnormalities
  - Maternal infection/endocrinopathy/coagulopathy
- Unexplained

Risk Factors for EPL

- Age
- Prior SAb
- Smoking
- Alcohol
- Caffeine (controversial)
- Maternal BMI <18.5 or >25
- Celiac disease (untreated)
- Cocaine
- NSAIDs
- High gravidity
- Fever
- Low folate levels
Normal Implantation & Development

- **Implantation:**
  - 5-7 days after fertilization
  - Takes ~72 hours
  - Invasion of trophoblast into decidua

- **Embryonic disc:**
  - 1 wk post-implantation
  - If no embryonic disc, trophoblast still grows, but no embryo (anembryonic pregnancy)
  - Embryonic disc embryonic/fetal pole

---

Milestone of embryology as assessed by TVUS

**Timing of first appearance of gestational landmarks on transvaginal ultrasound examination**

<table>
<thead>
<tr>
<th>Landmark</th>
<th>First appearance on transvaginal ultrasound examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational sac</td>
<td>4.5 to 5 weeks</td>
</tr>
<tr>
<td>Yolk sac</td>
<td>5 weeks</td>
</tr>
<tr>
<td>Cardiac activity</td>
<td>5.5 to 6 weeks</td>
</tr>
<tr>
<td>Measurable crown-  rump length</td>
<td>6 weeks</td>
</tr>
</tbody>
</table>

---

U/S Dating in Normal Pregnancy

- **Mean Sac Diameter (mm) + 30**
- **Crown-Rump Length (mm) + 42**

Clinical Presentation of EPL

- Bleeding
- Pain/cramping
- Falling or abnormally rising hCG
- Decreased symptoms of pregnancy
- No symptoms at all!
Transvaginal Ultrasound Findings of EPL

- Anembryonic Pregnancy
  - No fetal pole with mean sac diam ≥25 mm
  - Absence of embryo with heartbeat ≥2 wks after scan that showed a gestational sac without a yolk sac
  - Absence of embryo with heartbeat ≥11 days after a scan that showed a gestational sac with a yolk sac

- Embryonic Demise
  - No cardiac activity with CRL ≥5 mm
  - ≥7 mm for 100% specificity


Samantha

26 yo G2P1, CRL of 7mm but no cardiac activity

Samantha and her partner request information on all the treatment options. You confirm the rest of her history.

PMH: wisdom teeth removed

Ob Hx: term SVD without complication

All: NKDA

Management Options

**Do Nothing:** Expectant management

**Do Something:** Medical management

**Do Surgery:** Management with D&C

Patient Satisfaction

*Management of Early Pregnancy Loss*

- Meta-analysis: studies report high satisfaction with medical management
- **Caution:** Few studies looked at satisfaction

- Satisfaction depended on choice:
  - if women randomized: 55-74% satisfied
  - if women chose: 84-88% satisfied
  - Both were independent of method

Sotiriadis A, Obstet Gynecol 2005

Nanda K, Cochrane Database Syst Rev 2006

Sotiriadis 2005
Samantha
26 yo G2P1, CRL of 7mm but no cardiac activity

Samantha is uninterested in waiting for spontaneous passage, and chooses medical management of her early pregnancy loss.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Misoprostol</th>
<th>Vaginal Aspiration</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage requiring hospitalization with or without blood transfusion — % (no. total no.)</td>
<td>1 (9/88)</td>
<td>1 (1/148)</td>
<td>1.0</td>
</tr>
<tr>
<td>Hospitalization for endovacuum — % (no. total no.)</td>
<td>&lt;1 (2/468)</td>
<td>0 (0/348)</td>
<td>1.0</td>
</tr>
<tr>
<td>Fever (temperature ≥100°F [≥37.8°C]) — % (no. total no.)</td>
<td>3 (15/477)</td>
<td>4 (6/4/8)</td>
<td>0.41</td>
</tr>
<tr>
<td>Emergency visit to hospital within 24 hr after treatment — % (no. total no.)</td>
<td>3 (15/477)</td>
<td>2 (2/148)</td>
<td>0.19</td>
</tr>
<tr>
<td>Unplanned hospital visits — % (no. of visits/total no. of patients)</td>
<td>23 (114/488)</td>
<td>17 (25/148)</td>
<td>0.08</td>
</tr>
<tr>
<td>Change in hemoglobin between day 1 and day 11 — g/dL</td>
<td>-0.6±1.10</td>
<td>-0.1±0.89</td>
<td>0.001</td>
</tr>
<tr>
<td>Decrease in hemoglobin ≥2 g/dL — % (no. total no.)</td>
<td>9 (9/4/1)</td>
<td>4 (4/13/8)</td>
<td>0.03</td>
</tr>
<tr>
<td>Decrease in hemoglobin ≥3 g/dL — % (no. total no.)</td>
<td>5 (50/41)</td>
<td>1 (1/34/1)</td>
<td>0.04</td>
</tr>
<tr>
<td>Nausea — % (no. total no.)</td>
<td>53 (259/472)</td>
<td>29 (4/1/3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Vomiting — % (no. total no.)</td>
<td>20 (96/477)</td>
<td>7 (10/4/8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diarrhea — % (no. total no.)</td>
<td>24 (133/472)</td>
<td>10 (14/13/8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Abdominal pain — % (no. total no.)</td>
<td>99 (474/474)</td>
<td>95 (134/134)</td>
<td>0.001</td>
</tr>
<tr>
<td>Pain severity score</td>
<td>5.7±2.4</td>
<td>5.3±2.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Acceptability — % (no. total no.)</td>
<td>83 (375/451)</td>
<td>83 (127/153)</td>
<td>0.05</td>
</tr>
<tr>
<td>Would probably or absolutely recommend this procedure</td>
<td>78 (351/451)</td>
<td>75 (112/153)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Do Something
Medical Management

• Misoprostol
• Misoprostol + Mifepristone
• Misoprostol + Methotrexate

No medical regimen for management of EPL is FDA approved

Medical Management
Requirement for Therapy

• ≤13 weeks gestation
• Stable vital signs
• No evidence of infection
• No allergies to medications used
• Adequate counseling and patient acceptance of side effects
Misoprostol

- Prostaglandin E1 analogue
- FDA approved for prevention of gastric ulcers
- Used off-label for many Ob/Gyn indications:
  - Labor induction
  - Cervical ripening
  - Medical abortion (with mifepristone)
  - Prevention/treatment of postpartum hemorrhage
- Can be administered by oral, buccal, sublingual, vaginal and rectal routes


Why Misoprostol?

- Do something while still avoiding surgery
- Cost effective
- Stable at room temperature
- Readily available

Misoprostol Dosing Regimens

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creinin</td>
<td>400 mcg po vs 800 pv</td>
<td>25% vs. 88%</td>
</tr>
<tr>
<td>Ngoc</td>
<td>800 mcg po vs 800 pv</td>
<td>89% vs. 93% (NS)</td>
</tr>
<tr>
<td>Tang</td>
<td>600 mcg SL vs 600 pv q 3 hrs x 3 doses</td>
<td>87.5%</td>
</tr>
<tr>
<td>Phupong</td>
<td>600 mcg po x 1 vs. q 4 hrs x 2 doses (SL had more side effects—diarrhea, 70% vs 27.5%)</td>
<td>82% vs 92% (NS)</td>
</tr>
<tr>
<td>Gilles</td>
<td>800 mcg pv saline-moistened vs. dry</td>
<td>83% vs 87% (NS)</td>
</tr>
</tbody>
</table>


Pooled Outcomes

Medical Management

Success Rates

- Placebo 16–60%
- Single dose misoprostol 400–800 mcg 25–88%
- Repeat dose x 1 if incomplete at 24 hours 80–88%

Success rate depends on type of miscarriage:

- 100% with incomplete abortion
- 87% for all others

Serum Level Comparison
Misoprostol by Route of Administration

Side Effects and Complications
Misoprostol vs. Placebo

N/V, Diarrhea: Increased with misoprostol

Pain: More pain and analgesics in one study

Hemoglobin Conc: No difference

Infection: No statistical difference placebo vs. misoprostol

- No benefit with repeat dosing within 3–4 hours
- Improved outcome with 1 repeat dose at 24 hours, if incomplete
- 90% found medical management acceptable and would elect same treatment again


Misoprostol Bottom Line
Medical Management

- 800 mcg vaginal or buccal
- Repeat x 1 at 12–24 hours, if incomplete
  - Occasionally repeat more than once for successful completion

- Give pain medications
- High dose NSAIDS
- Small number Narcotics
- Anti-emetics as needed
- Follow Up in 1-2 weeks after treatment

Mifepristone and Misoprostol
Medical Management

- Mifepristone: Progestin antagonist that binds to progestin receptor
  - Used with elective medical abortion to “destabilize” implantation site
  - Current evidence-based regimen: 200 mg mifepristone + 800 mcg misoprostol

- Success rates for mifepristone & misoprostol in EPL:
  - 52–84% (observational trials, non-standard dose)
  - 90–93% (standard dose)

- No direct comparison between misoprostol alone and mifepristone/misoprostol with standard dosing
- Mifepristone probably helps, use if you can easily

Akhrem M, Fertility Sterility 2000; Schneider CA, Contraception 2000
Methotrexate and Misoprostol
Medical Management

- Methotrexate
  - Folic acid antagonist
  - Cytotoxic to trophoblast
- Used in medical management for ectopic pregnancy
- Introduced in 1993 in combination with misoprostol to treat elective abortion medically
  - Success rates up to 98% (misoprostol administered 7 days after methotrexate)
- No data for use in early pregnancy loss

Samantha
26 yo G2P1, CRL of 7mm but no cardiac activity

Samantha returns to the office 7 days after treatment with mifepristone and misoprostol for follow up.

How do you BEST assess whether or not her treatment is complete?
1. Repeat ultrasound
2. Serial serum beta-HCG tests
3. Urine pregnancy test
4. History and physical

How do you determine successful completion?
Definitions Used in Studies

- ≤15 mm endometrial thickness (ET) 3 days to 6 weeks after diagnosis
- No vaginal bleeding
- Negative urine hCG
Problems with ET Cut-off

• No clear rationale for this cut-off
• Study of 80 women with successful medical abortion
  • Mean ET at 24 hours 17.5 mm (7.6–29 mm)
  • At one week 15% with ET >16 mm
• Study of medical management after EPL
  • 86% success rate if use absence of gestational sac
  • 51% success rate if use ET ≤15 mm

Harwood R, Contraception 2001

Other problems with follow-up modalities:

• Vaginal bleeding and positive urine pregnancy test are possible for 2–4 weeks
• Poor measures of success at a 1-2 week follow-up visit
• Serial serum HCG tests —
  • Can check 2 to ascertain falling values then stop
  • Don’t need to follow to zero
• Bottom line:
  • Use ultrasound if available
  • If ultrasound not viable option, can check urine pregnancy test
  • If UPT positive, can check serum HCG and repeat ONCE if still elevated.

When to intervene after medical management?

• Continued gestational sac
• Stable/rising/inappropriately falling HCG
• Clinical symptoms
• Patient preference
• Time (?)

Samantha
26 yo G2P1, CRL of 7mm but no cardiac activity

At her follow-up appointment, Samantha says that she had a period of heavy bleeding and is now spotting. Her cramping has resolved. She has noted a marked decrease in breast tenderness and nausea.

Her ultrasound shows a uniform endometrial stripe measuring 30mm in its greatest width.
Samantha
26 yo G2P1, CRL of 7mm but no cardiac activity

Is Samantha’s pregnancy loss complete?
1. Yes
2. No

Future Risk of Early Pregnancy Loss

<table>
<thead>
<tr>
<th></th>
<th>1 SAb</th>
<th>2 SAb</th>
<th>3 SAb</th>
</tr>
</thead>
<tbody>
<tr>
<td>20%</td>
<td>28%</td>
<td>43%</td>
<td></td>
</tr>
</tbody>
</table>

Post EPL Care

- Rhogam at time of diagnosis or treatment
- Pelvic rest for 2 weeks
- No evidence for delaying conception
- Initiate contraception upon verification of completion
- Expect light-moderate bleeding for 2 weeks
- Menses return after 6 weeks
- Negative βhCG values after 2–4 weeks
- Appropriate grief counseling

When Women Should Contact Clinician

• Heavy bleeding with dizziness, lightheadedness
• Worsening pain not relieved with medication
• Flu-like symptoms lasting >24 hours
• Fever or chills
• Syncope
• Any questions

For more Information on EPL

• TEAMM website: www.miscarriagemanagement.org
• UCSF website: www.earlypregnancylossresources.org
• Association of Reproductive Health Professionals (ARHP) archived webinar: Options for Early Pregnancy Loss: MVA and Medication Management
www.arhp.org/healthcareproviders/cme/webcme/index.cfm
• Ipas WomanCare Kit for Miscarriage Management
www.ipaswomancare.com
• Papaya Workshop Videos: www.papayaworkshop.org

Thanks!

Questions
pragers@uw.edu
From Category A to X: Medication Use and Safety During Pregnancy

Alyssa Stephenson-Famy, MD
University of Washington
Department of Obstetrics & Gynecology
March 27, 2015

Overview of this talk
• Updates on FDA pregnancy category
• Review of embryology and physiology of teratogens
• Medication management: Anticipate pregnancy and provide counseling
  – Medications that are definitely bad
  – Medications that are generally safe
  – Necessary medications with minimal data
• Lactation resources

FDA Pregnancy Categories
• A – Controlled studies show no risk
• B – No evidence of risk in humans - animal studies show no risk and no controlled studies in pregnant women or some adverse effects in animals but not confirmed in humans
• C – Risk cannot be ruled out - animal studies show adverse effects and no controlled studies in humans; studies not available
• D – Positive evidence of human risk, but use may be acceptable if benefits outweigh risks
• X – Significant fetal risk, unsafe

Disclosures
• No disclosures
How useful were the labels?

- Pregnancy categories: antiquated, unhelpful
  - A = awesome
  - X = teratogenic
  - What did B, C and D really mean?

- 2008 FDA proposed removing the categories
  - Favoring a descriptive narrative
- 2011 FDA updated their website
  - Considering how and if they will adopt the proposal
- 2015 FDA updated their website with...

FDA.gov

Plan for Drug Labeling

- “The revised labeling will replace the old five-letter system with more helpful information about a medication’s risks to the expectant mother, the developing fetus and the breastfed infant.”
- “…the labeling will also include a subsection called ‘Females and Males of Reproductive Potential.’ This subsection will provide a consistent location for relevant information about pregnancy testing, birth control and a medication’s effect on fertility.”
Medication information

- Reprotox, Reprorisk (TERIS), OTIS – online
- Drug registries, drug company – most conservative
- Limitations of drug information
  - Baseline risk of birth defects
  - Limited studies – case reports and series
  - Reporting bias
  - Animal studies often species-dependent and cannot easily extrapolated to humans
  - Crossing placenta ≠ birth defects!!
  - Difficult to define drug effects vs. disease effects

- **Tip:** Lactmed – (lactation) download the app!

Label or no Label: What is important?

- What is definitely safe?
- What is definitely bad?
- For non-pregnant women using medications that are category C or worse
  - anticipate questions, problems
- For pregnant women using medications that are pretty much safe (category B and C)
  - approach to counseling
Quick review of embryology

Determining causality of teratogens

- What needs to be true?

Determining causality of teratogens

- Cross the placenta
  - Or could result from deranged maternal health/biochemical status
  - Or could result from compromised placental function
- Biologic plausibility
- Temporal relationship
- Dose response relationship
- Higher than baseline rate of birth defects (2-3%)
- Specific effect versus multi-organ system
Non-pharmacologic teratogens

- Although providers, patients and pharmacists are very worried about medication use in pregnancy...

What else can be bad for you in pregnancy that is not medication-related?

Teratogenic: Maternal Diabetes

<table>
<thead>
<tr>
<th>HgbA1c (%)</th>
<th>Fetal anomalies (%)</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;9.3%</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>9.4-11</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>11-12.7</td>
<td>8</td>
<td>2.5</td>
</tr>
<tr>
<td>12.8-14.4</td>
<td>33</td>
<td>10.7</td>
</tr>
<tr>
<td>&gt;14.4</td>
<td>40</td>
<td>13.4</td>
</tr>
</tbody>
</table>

Teratogenic: Maternal Diabetes

<table>
<thead>
<tr>
<th>Fetal Anomaly</th>
<th>Embryonic Age</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caudal regression</td>
<td>&gt;3 weeks</td>
<td>200X</td>
</tr>
<tr>
<td>Spina bifida</td>
<td>4 weeks</td>
<td>10X</td>
</tr>
<tr>
<td>Situs inversus</td>
<td>4 weeks</td>
<td>40X</td>
</tr>
<tr>
<td>Cardiac</td>
<td>5-6 weeks</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>5 weeks</td>
<td></td>
</tr>
<tr>
<td>Anal/rectal atresia</td>
<td>6 weeks</td>
<td></td>
</tr>
</tbody>
</table>

Teratogens: Recreational exposures

- Fetal Alcohol Syndrome
  - Most likely associated with heavy/binge drinking
  - Causes variety of fetal anomalies:
    - Cardiac, genitourinary, midface hypoplasia, short palpebral fissure, growth restriction, microcephaly, mental retardation

- Cocaine: vascular events → limb loss
Teratogens: Incidental exposures

Ionizing radiation:
- Critical period 8-14 weeks
- No risk <5 rads
- Threshold 10 rads
- Microcephaly 10-20 rads

<table>
<thead>
<tr>
<th>Study</th>
<th>Rad</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXR</td>
<td>0.001</td>
</tr>
<tr>
<td>V/Q scan</td>
<td>0.03</td>
</tr>
<tr>
<td>DEXA</td>
<td>0.6</td>
</tr>
<tr>
<td>Abd CT</td>
<td>0.8</td>
</tr>
<tr>
<td>Angiogram</td>
<td>2.5 rad</td>
</tr>
</tbody>
</table>

Good news: Dental X-rays are 0 rads!

Medication Use in Pregnancy

- Goal #1: avoid medication use in pregnancy
- If this not feasible, what are next goals?

Medication Use in Pregnancy

- Minimize medication use/dose for therapeutic effect
- Discontinuation of chronic medications in first trimester usually a BAD idea
- Look for an acceptable alternative
- Often drugs are necessary to protect the health and well-being of the mother AND to ensure the success of the pregnancy
  - Fetal well-being is dependent on maternal status
  - Balance of risks and benefits

What is bad (Category X)?

- What is the most famous teratogen?
Thalidomide

Limb reduction defect: phocomelia

Thalidomide vs. Bendectin

Doxylamine + Pyridoxine (B6) = Bendectin Diclectin

Care compromised by controversy

Hospitalizations for N/V

Limb reduction defects

Prescriptions for Bendectin

Category A: good marketing

HOW SAFE IS DICLEGIS®?

DICLEGIS® has been developed with the safety of mother and baby in mind. DICLEGIS® has been tested and studied in pregnant women.

DICLEGIS® has a Pregnancy Category A status, the best rating available.

Each DICLEGIS® tablet shows a pregnant woman because it was created for you.

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Studies in pregnant women have shown that the medicine does not present an increased risk to the baby.*</td>
</tr>
</tbody>
</table>

*Although no harm has ever been observed, you should still speak to your healthcare provider about any potential risks.
Safe (Category A) Medications

- Prenatal vitamins
  - Category C if exceeds RDA of folate, B12, C, E, B6, B1
  - Category X if exceeds RDA of Vitamin A
- Folic acid
- Vitamin B6 and doxylamine
- Levothyroxine, cytomel, armour thyroid
- Nystatin vaginal preparation

Safe (Category B) Medications

- Benadryl, tylenol
- Lovenox
- Hydrochlorothiazide
- Metformin, glyburide, insulin
- PPI, H2-blockers, ondansetron, reglan
- Most antibiotics

Early Pregnancy Patient Scenarios

- 24 year old on warfarin for a DVT
- 38 year old on methotrexate for rheumatoid arthritis

Teratogenic Medications

- Coumadin
  - 1st trimester: embryopathy and fetopathy
  - Nasal hypoplasia, shortened limbs, IUGR, deafness, scoliosis, microphthalmia
- Methotrexate
  - Craniofacial, skeletal, cardio-pulmonary and GI, developmental delay, miscarriage
- Acutane (isoretinoids)
  - Affects CNS, cardiovascular, endocrine systems
- Thalidomide
  - Phocomelia, etc. Critical window 4-6 weeks
Early Pregnancy Patient Scenarios

- 16 year old on doxycycline for acne
- 42 year old on statin and ACE inhibitor for metabolic syndrome
- 28 year old on lithium, seroquel, lamictal for bipolar

Teratogenic Medications

- ACE-I (all trimesters): *Data conflicted!*
  - Oligohydramnios, anuria, renal failure, PDA, aortic arch obstructive malformations, fetal death
- Statins: *Stay tuned for possible therapeutic uses!*
  - Fetal cells are made up of maternal lipids, pregnancy normally increases all lipids
- Valproic Acid, Carbamazepine, Phenytoin
  - Craniofacial defects, limb abnormalities, heart defects, neural tube defects, cleft palate
- Lithium
  - Fetal arrhythmias, hypoglycemia, polyhydramnios, “floppy infant” syndrome
  - ? Ebstein’s anomaly

Teratogenic Medications

- Antibiotics to avoid:
  - Tetracycline (doxycycline): permanent discoloration of teeth, enamel hypoplasia
  - Quinolones (ciprofloxacin, levofloxacin): joint concerns
- Safe:
  - Nitrofurantoin, sulfonamides → OK for use in the second and third trimester, acceptable for use in the first trimester if no other alternative
  - Metronidazole
  - PCN and cephalosporins
  - Macrolides

Early Pregnancy Patient Scenarios

- 35 year old on plaquenil and prednisone for SLE
### Rheumatologic Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Category</th>
<th>Pregnancy Risks</th>
<th>Lactation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxychloroquine (Plaquenil)</td>
<td>C</td>
<td>Crosses the placenta (Caution)</td>
<td>Compatible with BF</td>
</tr>
<tr>
<td>Sulfasalazine (5-ASA)</td>
<td>B</td>
<td>Crosses the placenta</td>
<td>AAP &quot;use with caution&quot;</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>C/D</td>
<td>Oligohydramnios, premature constriction of DA</td>
<td>Ibuprofen preferred</td>
</tr>
<tr>
<td>ASA (81 mg vs. 325 mg)</td>
<td>C/D</td>
<td>IUGR, bleeding, acidosis, premature closure of DA</td>
<td>High dose “avoided”, low-dose “considered”</td>
</tr>
<tr>
<td>Prednisone</td>
<td>B</td>
<td>Clefts, PPROM, IUGR, GHTN, GDM, osteoporosis, infection</td>
<td>No concerns with dose &lt;20 mg</td>
</tr>
<tr>
<td>Azathioprine (Imuran), 6-MP</td>
<td>D</td>
<td>Mixed anomaly data, risks higher in transplant</td>
<td>Lactmed &quot;usually acceptable&quot;</td>
</tr>
</tbody>
</table>

---

### Excretion of drugs in breast milk

- Most drugs molecular weight 200-500 kDa
- Some secretion if MW > 1000 kDa
- Readily if MW < 600 kDa
- Amount in milk dependent upon:
  - Maternal plasma concentration
  - Protein binding
  - Lipid solubility
  - Ionization at physiologic pH

---

So you are going to continue a medication in pregnancy...
Drugs in Lactation

- **Drugs that are contraindicated**
  - Chemotherapeutic agents (may BF in between cycles)
    - Cyclophosphamide, cyclosporine, doxorubicin, MTX
  - Drugs of abuse: methamphetamine, cocaine, heroin, PCP
  - Radioactive compounds
- **Drugs should be used with caution:**
  - Acebutolol, 5-ASA, Aspirin, Atenolol, Ergotamine, Lithium, Phenobarbital, Pseudoephedrine, Primidone, Sulfasalazine,
- **Drug effect unknown but may be of some concern:**
  - Anxiolytics, some SSRIs and antipsychotics, amiodarone, metronidazole, tinidazole, chloramphenicol, lamotrigine
Recurrent Pregnancy Loss: 
Evaluation and Management for the 
Primary Care Provider

Lora Shahine, M.D., F.A.C.O.G. 
Pacific NW Fertility and IVF Specialists 
Clinical Faculty University of Washington

Women's Health Care Update
March 27, 2015

Objectives
- Definitions of pregnancy and RPL
- Evaluation of RPL
- Management of Unexplained RPL

Question 1
How Many Miscarriages before an evaluation should begin?

- 1
- 2
- 3
- 4

Background
Definitions
- Pregnancy – a clinical pregnancy documented by ultrasound or histopathologic examination
- RPL - a disease distinct from infertility, defined by 2 or more failed pregnancies for purposes of clinical evaluation
- RPL for epidemiological studies should be defined as 3 or more miscarriages

ASRM Committee Opinion, Fertility and Sterility Jan 2013
Background

Incidence
• 15-25% of clinically recognized pregnancies will result in loss
• <5% of women will have 2 consecutive miscarriages
• 1% of women will experience 3 or more miscarriages

ASRM Committee Opinion, Fertility and Sterility Jan 2012

Question #2
What is the most common cause of miscarriage?
• Blood clotting issue
• Immune issue
• Unexplained
• Uterine issue

Causes of RPL

Evaluation of RPL - History

• Thorough history and physical
  – Age, BMI
  – Obstetric history, timing of loss, testing on POC
  – Menstrual cycles
  – Patient and FHx clotting disease
  – Medical history – diabetes, thyroid disease

Other includes: endocrine disorders, obesity
Evaluation of RPL - Testing

- Uterine cavity evaluation (15%)
- Parental Genetics (Karyotype) (5%)
- Antiphospholipid Syndrome (15%)
- Hormonal factors (15%)

- What about the other 50%?

Uterine Cavity Evaluation

- Hysteroscopy, Hysterosalpingogram (HSG) or Saline Infusion Sonogram/sonohystogram
- Evaluating for congenital anomalies (septum) and submucosal fibroids

Parental Karyotypes

- Karyotype for both parents
- Looking for a balanced translocation
- 5% of couples with 3+ miscarriages
- Risk of live birth with unbalanced translocation

Antiphospholipid Syndrome

- 5-20% patients with RPL test positive for aPLs
- Autoimmune process
  - Various effects on the development of the developing placenta leading to early and late pregnancy loss
- Who should be tested?
  - Patients with 3 or more unexplained first trimester miscarriages <10 weeks
  - Patients with a single loss 10+weeks
  - Birth <34 weeks with severe pre-eclampsia, placental insufficiency

Antiphospholipid Syndrome: Testing

- Tests
  - Lupus anticoagulant (aPTT and dilute Russell's viper venom time)
  - Anticardiolipin IgG and IgM antibodies
  - Anti-B2-glycoprotein IgG and IgM antibodies
  - All other antibody testing not standardized and if test, increase false positive rate
- >6 weeks after negative bHCG
- Positive twice, 12 weeks apart

ACOG bulletin No 118 January 2011

Hormonal Factors

- Diabetes
  - HbA1C
- Prolactin
- Ovarian reserve testing
  - Cycle Day 3 FSH and estradiol
- Thyroid
  - TSH <2.5
  - TPO antibodies – controversial

Hypothyroidism and RPL

- Hypothyroidism (including subclinical) associated with poor obstetric outcomes including miscarriage
- Maternal thyroid function essential up to 20 weeks gestation
- 30% increased demand on maternal thyroid with pregnancy
- Recommend TSH <2.5 in women trying to conceive

Hypothyroidism and RPL

- Maternal thyroid function essential up to 20 weeks gestation
- 30% increased demand on maternal thyroid with pregnancy
- Recommend TSH <2.5 in women trying to conceive

Testing Not Recommended

- Cultures for bacteria
- Endometrial biopsies for luteal phase defect
- Male factor
- ANA
- HLA typing
- Embryotoxic factors
- Decidual cytokine factors
- Blocking or anti-paternal antibodies
- HLA-G polymorphisms and other immunologic traits
- Progesterone levels
- Thrombophilia
Progesterone

- Essential for implantation
- Ovulation dysfunction/inadequate P4/luteal phase defect
- Progesterone production is sporadic
  - Levels can be falsely reassuring or falsely worrisome
  - Poor progesterone levels associated with poor prognosis pregnancies – ectopic/miscarriage
- Progesterone support recommended regardless of lab results

Question 3
Thrombophilia testing (FVL, prothrombin gene mutation, etc.) is a part of a standard evaluation for RPL?

- True
- False

Inherited Thrombophilia

- FVL, Prothrombin gene mutation, Protein C, Protein S, and AT 3 deficiency
- Screening justified if personal history of blood clot or first degree relative with thrombophilia otherwise not recommended by ACOG and ASRM
- Kaandorp 2010 – RCT 364 patients with unexplained RPL
  - Aspirin vs. aspirin + heparin vs. placebo
  - Live birth rate not improved with intervention over all and in the subgroup of patients with inherited thrombophilia (47 patients)

Unexplained RPL

50% of couples with RPL will not have an identifiable cause for their losses and have unexplained recurrent pregnancy loss (Stephenson 1996; Jaslow 2010)
Aneuploidy and RPL

- 60-80% of SABs have aneuploidy
- Rate of miscarriage and aneuploidy increases with age, DOR, and history of RPL
  - 50% pregnancies end in SAB at age 40
  - 80% SABs >35 yo with RPL = aneuploid


Treatment for Unexplained RPL

- Expectant Management
- Supportive care
- Psychological support
- Lifestyle changes
- Empiric treatment
  - Aspirin
  - Progesterone
- IVF with PGS
  - Screening embryos for aneuploidy before conception

Preventing Aneuploidy: IVF/PGS

Old
- Biopsy 1-2 cells on Day 3
- FISH testing maximum of 9 chromosomes
- Transfer in the same cycle as egg retrieval
- Lower implantation rate

New
- Biopsy 4-5 cells on Day 5-6
  - Decrease risk of mosaicism
- CGH or microarray testing of all 24 chromosomes
  - Test all chromosomes
- Cryopreserve embryos after biopsy for future transfer
  - Allow for recovery before pregnancy
  - Vitrification has revolutionized cryopreservation

Blastocyst biopsy of 4-5 cells from trophectoderm

Technology of genetic testing developing
Evidence for IVF/PGS for RPL

- Hodes-Wertz 2012
  - 287 IVF cycles RPL patients (2+ losses)
  - 192 cycles Day 3 biopsy, 94 cycles Day 5 biopsy
  - Aneuploidy rate 53% embryos (average age 35)
  - Expected SAB risk 33.5% by age and history vs. observed loss 6.9% (P<0.1)

Prognosis
Unexplained RPL, No intervention

<table>
<thead>
<tr>
<th>Maternal Age</th>
<th>2 prior losses</th>
<th>3 prior losses</th>
<th>4 prior losses</th>
<th>5 prior losses</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Brigham SA. Hum Rep 1999

Expectant Management: Lifestyle changes

- Quit smoking
- Ideal weight (Goal BMI 19-25)
- Alcohol >3-5 drinks/week, higher risk of SAB
- Caffeine >3 cups of coffee/day higher risk of SAB

Expectant Management: Psychological factors

- RPL has significant emotional and psychological impact
- Small, observational studies have shown benefit of ‘TLC care’
  - Close monitoring with bHCG levels and first trimester ultrasound monitoring
Empiric Treatment

- Aspirin 81mg daily
  - Theoretical benefits for suppressing immune system, increasing blood flow to uterus and ovaries, first line treatment in aPLS
- Progesterone supplements
  - Important for implantation
  - Some evidence for benefits in patients with RPL
  - No evidence of harm with supplementation, number needed to treat likely high
- Start both with positive pregnancy test

Aneuploidy in POC

For
- 60-80% miscarriages have a chromosomal abnormality
- Provides an answer, reason for loss
- Patients can try again
- Treatment available: PGS
  - CGH
    - No cell culture
    - No maternal cell contamination

Against
- Cost
- Prognosis good with or without the information
- Limited information

Summary: RPL Care for Primary Care Provider

- Educate
  - Chance of another loss, causes, most common cause of loss is aneuploidy
- Evaluation
  - Discover and address any identifiable cause of miscarriage
- Supportive Care
  - Encourage confidence to try again
  - Aspirin and progesterone in first trimester
  - Early monitoring and support, test POC of subsequent loss

Summary

- Definitions of RPL – consider evaluation with 2 losses
- Testing for thrombophilia rarely indicated
- 50% of patients with RPL - unexplained
- High rate of aneuploidy in miscarriage
- IVF with PGS is an option to consider but current evidence limited
- High chance of live birth in most patients with no intervention, supportive care
Thank you!
Lora Shahine, M.D., F.A.C.O.G.
lshahine@pnwfertility.com
Women Veterans: An emerging health population in and outside the VA

UW Women’s Health Conference
3/27/15

Presented by Joyce Wipf, MD
UW Professor of Medicine
MD Director, Center of Excellence in Primary Care Education, VA Puget Sound

Why this topic?

• Women Veterans’ (WVs) important contributions in the military
• Champion for expanding VA comprehensive women’s health
• Rapidly growing # of WV
  • Changing “face” of US military and veterans
  • We all are/will be caring for WV
• Discuss special needs of Women Veterans’ population so we all can better address their health

Who are Women Veterans?

• Women Veterans are as diverse & heterogeneous as any health population
  • Can’t pigeonhole
  • Highly variable military experiences
  • Post-deployment evaluation
  • Special attention to hx sexual trauma, military-related conditions
  • Broad array of conditions/dx
    • Interesting women’s health; all ages; younger pts pregnancy planning follow up post-delivery, etc
• WV care high VA priority: increasing resources for access, comprehensive primary care, space, privacy, etc

Women Veterans

I. Growth
II. Post-deployment evaluation
III. Unique military experiences
IV. Special conditions
  • Military sexual trauma
V. Pregnancy and baby care
VI. Homelessness
Growth in population of Women Veterans

- Women are the fastest growing segment of the VA population
  - 15% active soldiers are women
  - Number WV expected to double in 5 yrs
  - % Women utilizing VA more than men (OIF/OEF)

- Currently 2.2+ million Women Veterans in US
- >68,000 in WA state (Alaska 8406, Idaho 6957)

*2014 VISN20/ national data

Population of Women Veterans
(Data Dr. Hayes, National VA WV Program, projections 2014, already exceeded # by 2013)

What percentage of Air Force active duty soldiers are women?

A. 10%
B. 15%
C. 18%
D. 20%
E. 24%
F. 28%
<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
<th>3/23/2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>What percentage of Air Force active duty soldiers are women?</td>
<td>A. 10% B. 15% C. 18% D. 20% E. 24% F. 28%</td>
<td></td>
</tr>
<tr>
<td>What percentage of Army active duty soldiers are women?</td>
<td>A. 10% B. 15% C. 18% D. 20% E. 24% F. 28%</td>
<td></td>
</tr>
<tr>
<td>Post-Deployment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
A New Generation: OEF/OIF (national data, Hayes 6/10)

- 128,397 separated female OEF/OIF Veterans since 2002
- Young – 46% less than 29; 78% less than 39
- 50% enrolled in VA

Pre-Military Life:
Psychosocial Risk Factors

Pre-military life is recent vs. remote
Context of deployment may have been stressful (ie reservists may have been "settled" prior to deployment)

Why did she join the military?
Screen for the following:
- Living environment
- Supportive relationships
- Significant life events
- Mental health history, substance abuse, child abuse

Post-Deployment:
Reintegration into Civilian Life

Steve Hunt, MD
VA Puget Sound Health Care System
Natara Garovoy, PhD, MPH
VA Palo Alto Health Care System
J Wipf Adapted for CoE

Recognize women veterans’ unique and complex health needs
Deployment risk factors?

**Deployment:**

- Changing Roles for Women
  - Serving in combat support units
    - Gunners, police, pilots, truck drivers, fuel suppliers
  - Exposed to unpredictable warfare
    - Improvised explosive devices (IEDs)
  - Daily operations
    - Equipment and gear: ceramic vests
    - Facilities
    - Health care: hygiene, diet
  - Exposed to military sexual trauma
    - Perpetrator may be a soldier in her unit

What about my feet, doctor?

(military shoes not specially designed for women)

Medical Diagnoses in Female OEF/OIF Veterans in VA Summary past decade

n=51,344

- Musculoskeletal: 50%
- Ill Defined Conditions: 48%
- Mental Disorders: 44%
- Nervous System/Sense Organs: 36%
- Digestive System: 35%
- Genitourinary System: 35%
- Endocrine System: 28%
- Respiratory System: 29%
- Diseases of Skin: 22%
- Injury/Poisonings: 22%
- Infectious and Parasitic Diseases: 16%
Mental Health Disorders among Female OEF/OIF Veterans Seen in the VA

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjustment reaction</td>
<td>58%</td>
</tr>
<tr>
<td>Depressive disorders</td>
<td>47%</td>
</tr>
<tr>
<td>Anxiety, adjustment, dissociative, mood, somatoform disorders</td>
<td>36%</td>
</tr>
<tr>
<td>Nondependent drug abuse</td>
<td>31%</td>
</tr>
<tr>
<td>Affective psychosis</td>
<td>28%</td>
</tr>
</tbody>
</table>

PTSD Rates and Risk Factors Among Female Veterans

- Women 2x Men in frequency of PTSD diagnosis
- Prevalence is 15-17% among OEF/OIF Veterans
- Co-morbid substance use
  - Binge drinking common in OEF/OIF Veterans
- Suicidal ideation
- Risky behaviors (e.g., unsafe relationships, eating disorders)
- Often presents as medical complaints (e.g., sleep difficulties) or psychosocial stressors

At risk for other post-deployment medical conditions

- Dental Disorders
- Vision
- Hearing Loss

35% of female veterans seen at the VA were diagnosed with genitourinary disorders

- Menstrual disorders
- Inflammatory Diseases of cervix, vagina, vulva
- Non-inflammatory disorders of cervix
- Disorders of the urethra
- Pain associated with female genital organs
- Disorders of breast
Post-Deployment Reintegration Stressors

- Concern for soldiers still deployed
- Feeling responsible for past duties
- Redeployment
- Housing
- Finances

- Unemployment
- Adjusting to civilian lifestyle
- Resuming family roles/responsibilities
- Reconnecting
- Feeling unable to talk about experiences; feeling alone

Addressing Post-Deployment Issues in Primary Care

- Patients are likely to first present in primary care
- An important opportunity for:
  - Early detection
  - Risk reduction
  - Addressing mind and body health
  - Facilitating referrals
  - Multidisciplinary Clinic helpful (Primary care, MSW, MH, GYN, Pharm, dietician, etc)

Each Woman Veteran has had a unique military experience

US Military: Women informally in “combat” roles

- All wars women supported combat (nursing, clerical before Gulf War)
- US Policy excludes women from ground combat, any direct operations
- 1995 Congress eased rules to allow female soldiers in 90% of military occupations
  - Officially barred direct combat (ie Marine/Army infantry) until Jan 2013
In fact women have been/are serving in direct combat ground operations in Iraq and Afghanistan; no “front line”

**US Military: Women informally in “combat” roles**

Each Woman Veteran has had a unique military experience:
important to individualize

- Women Veterans are as likely to report combat as male Veterans (~20%) (2009-10 data)
  - No front line in Afghanistan or Iran

- New rules Jan 23, 2013 allowing combat probably will only modestly change risk, but will increase opportunities for leadership, promotion, etc.

---

**Special Issues**

**Sexual Trauma**
What Is Military Sexual Trauma (MST)?

(summary slides Julia Sewell, VA PS MST Coordinator)

• VA term for sexual assault or sexual harassment occurring during military service

• Definition in Public Law:
  “Physical assault of a sexual nature, battery of a sexual nature, or sexual harassment” ["repeated, unsolicited verbal or physical contact of a sexual nature which is threatening in character"] that occurred while a veteran was serving on active duty or active duty for training

What Is MST? - 2

• Sexual assault: Any sort of sexual activity in which someone is involved against his or her will. This occurs when:
  - Someone is coerced into participation (e.g., with threats; “command rape”)
  - Someone is not capable of consenting to participation (e.g., when intoxicated)
  - Someone is physically forced into participation

  * Physical force may or may not be used.

What Is MST? – 3

• Sexual harassment: Repeated, unsolicited, and threatening verbal or physical contact of a sexual nature

  Examples include:
  - Implied faster promotions or better treatment in exchange for being sexually cooperative
  - Implied negative consequences for refusing to be sexually cooperative
  - Unwanted sexual attention, such as cornering, touching, or verbal remarks

MST Support Team Screening Report

<table>
<thead>
<tr>
<th></th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Screened Positive</td>
<td>20%</td>
<td>1%</td>
</tr>
<tr>
<td># Screened Positive</td>
<td>48,000</td>
<td>44,000</td>
</tr>
</tbody>
</table>

National All Veteran Data FY 2010 (similar 2011-12)
VA Puget Sound
Rates of MST

- VA PSHCS twice national average:
  (similar annual data 2010, 2011, 2012)
- publicized June 2012, Sen Murray hearings→press
  regionally and nationally
  - 2.7% men report MST (1.1% national average)
  - 40.9% women report MST (21.9% national average)

WHY?

Uncovering MST

- Note 20% of Women are sexually assaulted while in the military
- Estimated 500,000 cases
- Many women experienced punitive consequences for
  reporting MST; rarely for perpetrator
- 2 days after viewing the video, Sec Leon Panetta removed from
  unit commanders the decision re: pursuing MST cases

Video on experiences of Women Veterans 2013
Producer Emmy-award winning film-maker Marcia Rock

Includes stories from WV with MST, PTSD, physical
disabilities, other; Filmed in part at Seattle Women’s Clinic

MST - Symptoms

Some Common Physical Symptoms of
Sexual Trauma Survivors Are...

- STDs
- Chronic pain (e.g. back pain, headaches)
- Gastrointestinal Disorders
- Gynecological Problems: 5% get pregnant
- Dissociation/memory loss
- Non-specific immune-system disorders
  (Chronic Fatigue Syndrome, Lupus, Fibromyalgia)
MST - Symptoms
Common Emotional Symptoms are:
- Anxiety
- Depression
- Panic
- Rage
- Shame
- Guilt

MST - Symptoms
Sexual Trauma Survivors Have Increased Health Risks Such As...
- Eating disorders/ obesity
- High risk behaviors: risky driving, substance abuse, sexual behaviors
- Poor compliance with treatment
- Major depression
- Somatization
- Self-mutilation/ Suicidal ideation or attempts

MST - Assessment
Strategies for Making Inquiries
- Create a context for the assessment
  - Privacy!
  - Confidentiality!
  - Empathy!
- Normalize
  - “Unfortunately, violence is common in our society, so I ask all my patients about this…”

MST - Assessment
Referring Patients to Mental Health Services
- Referral in a way to maximize acceptability
- Normalize: “Many of my patients, who have had similar experiences, have found it helpful to speak with a counselor”
- “We have specially trained staff available; would you like to speak with someone?”
- Educate patients about referrals and resources
  - Reassure patient that the referral is their choice
**MST Screening**

- All treatment (including medications) for physical and mental conditions related to MST → free care at the VA (ie no pharmacy co-pay)
- All veterans seeking VA care must be screened for MST
  - OK to rescreen, some not ready to disclose initially

**Combat-related Exposure**

- Problems similar to those for sexual assault
- Drug-related disorders
- Accidental deaths
- Higher level of general psychiatric distress
- More frequent somatic complaints
- Anxiety/panic
- PTSD

**Caregivers and Veterans Omnibus Health Services Act of 2010 (Public Law 111-163)**

The VA covers “post-delivery and routine care” for the first 7 days of the infant’s life (effective 5/5/2010)

**Homelessness among Women Veterans**
Homelessness
Active Outreach/ Awareness

- Women Veterans are becoming homeless at a faster rate than male Veterans
- Risk factors include:
  - Unrecognized mental health issues
    - PTSD and adjustment disorders more common
    - Sexual trauma
    - Undocumented combat stress
    - Hidden substance use
  - Lower income and earnings than men

Homelessness - 2

- National VA goals:
  "No veteran should be homeless"
  - Ambitious programs/interventions/housing
- Homeless programs expanding to meet needs of women with children
- Increased screening for PTSD, depression, substance use
- Integration of MH in PC allows evaluation for risk of homelessness (tools under development)

"I'm so proud of the Women Veterans I know: they manage life-work-family challenges like every other woman, and if negative military experiences, have long-lasting effects. Yet they are strong, resilient, and keep trying to get help and move forward!"

Thank you
Additional References – 1


THE KNEE- Narrowing differential to facilitate appropriate management

Overview
- Quick anatomy
- Key exam points
- Imaging
- Narrowing differential and making appropriate management decisions

Menisci
- Medial and Lateral
- Function
  - Increased articular surface area and "chuck" for stability
- Injury/menisectomy increases risk for subsequent arthritis

Collateral Ligaments
- Extra-articular
- Medial
  - 80% valgus stability
  - Most commonly injured and high healing potential
- Lateral
  - 70% of varus stability
  - Rarely isolated injury
Anterior Cruciate Ligament

- Opposes ant. tibial translation, rotation
- Commonly injured in female teenage athletes
- Little healing potential
- Often surgically reconstructed

Posterior Cruciate Ligament

- Opposes posterior tibial translation, rotation
- Injured with fall on anterior tibia or dashboard
- Better healing potential than ACL and difficult to anatomically reconstruct

Key muscles in knee function

- VMO
  - Absorbs eccentric load and controls patellar tracking
- Gluteus medius and hip ext. rotators
  - Controls knee rotation and valgus alignment
- Hamstrings
  - Prevent anterior tibial translation which protects ACL

Physical exam

- Inspection
- Range of motion
- Palpation
- Smoothness
- Strength
- Stability
Physical Exam

- Inspection
  - obvious deformity or swelling
  - Standing alignment: hips through feet
    - Assess dynamic alignment with single leg squat
      - Functional Trendelenburg
      - Excessive knee internal rotation

- Palpation for effusion
  - 2 methods
    - Milk fluid from one side to other
    - Palpate fluid wave

Physical Exam - Stability

- Medial / Lateral collateral ligaments
  - Control hip rotation by placing foot under arm
  - Injury causes pain with testing and asymmetric laxity

- Posterior cruciate ligament
  - posterior drawer
    - note "sag sign" if present
    - grade 1: increased translation, soft endpoint
    - grade 2: tibial plateau even with femoral condyles
    - grade 3: plateau posterior, no firm endpoint
Physical Exam- Stability

- Anterior cruciate ligament
- Lachman’s test
  - Relaxation essential, so be gentle
  - Laxity varies but should be symmetric
  - Torn ligament lacks firm endpoint

Physical Exam- McMurray's

- thumb- MJL, long finger- LJL
- flex knee, internal and external rotation
- extend knee with varus then valgus with leg in internal and external rotation
- Click, pop, or pain is + test

Imaging- Plain XR WB

Notch view-normal  AP- Medial OA

Imaging

- MRI
  - Soft tissue detail
  - Excellent for tumors
  - Bone detail inferior to CT
  - NOT 100% sensitive
    - Familiarity with reading and good exam skills pre-requisite

Sagittal- discoid torn meniscus
Key variables to triage and diagnose patients with knee pain

- Mechanism
  - Acute traumatic (suspected internal derangement) versus overuse/biomechanical presentation
- Location of pain
- Presence or absence of effusion
- Weight bearing x-ray
- Clinical scenario c/w inflammatory arthropathy

Suspected internal derangement

- Key features
  - history of trauma
  - swelling
  - instability
  - mechanical symptoms
- Imaging
  - Initial visit: XR or MRI depending on clinical concern
- Consultation
  - Sports Med/Orthopaedist

Suspected internal derangement

- Diagnoses
  - Meniscal tears: acute or chronic degenerative
  - Ligamentous injury in order of frequency
    - MCL, ACL, PCL, LCL
  - Patellar dislocation
  - Intraarticular fracture
  - Osteochondritis dessicans in adolescents

Overuse / Biomechanical

- Key Features
  - insidious onset, no trauma
  - history of "training error"
  - no effusion or significant mechanical symptoms
  - worse with activity, improves with rest
- Imaging
  - Rarely at initial visit
  - Caveat: joint pain >age 50 should be x-rayed
- Consultation
  - Physical Therapy
Overuse / Biomechanical

- Diagnoses
  - Chondromalacia/patellofemoral pain
  - Iliotibial band tendonitis
  - Patellar tendonitis
  - Distal hamstring tendonitis
  - Plica syndrome

Differential Diagnosis by Location

- Anterior
  - Patellofemoral/chondromalacia
  - Patella tendonitis

- Lateral
  - Iliotibial band tendonitis
  - Lateral meniscal tear
  - Lateral plateau fracture
  - Lateral compartment DJD

- Medial
  - MCL sprain
  - Medial plateau fx
  - Medial meniscus tear
  - Medial compartment DJD
H and P ortho variables in knee pain: ? Need for early imaging or referral

- Concerning
  - Trauma/injury
  - Locking
  - Swelling/effusion
  - Acute loss of motion
  - Instability
  - Unable to bear weight
  - Joint line tenderness
  - Asymmetric AP, lateral, or rotational laxity on exam

- Reassuring
  - History of overuse
  - Worse with activity, better with rest
  - Anterior pain
  - Isolated medial laxity without effusion

Internal derangement- treatment

- Majority of surgical problems
  - ACL depending on activity and individual
  - PCL with instability and grade 2+ laxity
  - Meniscal tears with locking or persisting pain
  - Recurring patellar dislocation
  - Symptomatic articular cartilage injury
  - Intraarticular fracture with displacement

ACL Tear-Treatment

- Little healing potential but some “cope” without ACL.
- Rehabilitation to restore motion and progressively strengthen/stabilize hamstrings, hips, core
- Reconstruction
  - Stabilization- indication instability or desire RT high risk activity, favored in younger athletes
  - Allow return to high risk sports
  - Protect against meniscal tear from subsequent episodes of instability

Overuse / Biomechanical Treatment

- Rest and ice
- Local / systemic anti-inflammatory treatment
- Identify mechanical / kinetic chain deficits
- Rehab directed to correct deficits
  - Excessive pronation
  - Tight quads, hamstrings, ITB
  - Strengthen quads, emphasize VMO and eccentric strength
- Advance to sport specific skills
Knee Osteoarthritis Treatment

• Ice/heat, acetaminophen then NSAIDS
• ROM and encourage lower impact exercise
• Weight loss
• Heel wedges and unloader bracing for uni-compartmental disease
• Joint injection
  – Cortisone and viscosupplementation
• Consult for joint replacement surgery

A 24-year-old female complains of a knee injury sustained yesterday. She was playing soccer when she was hit from the side landing on her left knee. She thinks she felt or heard a pop. It was quite painful initially but after about half an hour felt much better. She does note her knee is fairly swollen and feels somewhat unstable. The most likely diagnosis is?

• A: Meniscal tear.
• B: Anterior cruciate ligament (ACL) tear.
• C: Chondromalacia patella.
• D: Iliotibial band syndrome

A 24 female complaints of knee pain. She is training for her first marathon and noted toward the end of an 18-mile run sharp pain in the lateral aspect of her knee. She had to stop running. Between runs it is okay but running even a mile is now very painful and she has to stop. She’s not aware of any swelling. Her most likely diagnosis is?

• A: Meniscal tear.
• B: Anterior cruciate ligament (ACL) tear.
• C: Chondromalacia patella.
• D: Iliotibial band syndrome
A 45 year old female complains of left medial knee pain worse with activity and some AM stiffness. It is worse since ski season started and now noting some swelling. She had “terrible triad” knee injury 15 years ago skiing which was surgically addressed. Since then she has done pretty well until recently. No significant instability or locking. Imaging at this visit should include ?

- A: none
- B: x-ray
- C: MRI
- D: CT

A 33-year-old female presents complaining of pain in the anterior medial aspect of her knee. She runs 3 to 5 miles a few times a week and the pain is gradual in onset. She finds that it improves with rest but is painful and stiff getting up after sitting for a prolonged period. She describes some “noise” particularly with stairs but no significant swelling or instability. Otherwise she is in good health. What is the most appropriate initial management ?

- A: xray, ice after activity, PT referral
- B: no imaging, ice after activity, PT referral
- C: MRI, ice after activity, PT referral
- D: MRI, ice after activity, Orthopedic consult
Management of Menopause Symptoms
Eliza Sutton MD
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Associate Professor, Dept of Medicine, UW
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Disclosures
- I have no financial conflicts of interest to disclose
- I will be discussing off-label use of some medications & have used an asterisk * to so indicate
- Pricing information reflects Average Wholesale Price from Up To Date, accessed 3/16/2015 – not the cost charged by pharmacy, nor patients' copay

Objectives
- Recognize menopause-related symptoms: menstrual, vasomotor, & genitourinary
- Develop, expand, or confirm your repertoire of treatment options
- Be aware of newer medications for menopause symptoms including their benefits & drawbacks compared with existing medications

What is menopause?
- Definition: Cessation of natural menses due to loss of ovarian function, defined historically by 1 year of amenorrhea after the FMP (final menstrual period)
- Commonly used to refer to transition period from up to several years before the FMP to years thereafter
- Related terms:
  - Premature menopause, premature ovarian failure
  - Perimenopause or menopause transition
  - Postmenopause
What is menopause?

- Menstrual definition relies on menstrual pattern as marker of ovarian function
- Symptoms (including menstrual changes) are due to hormonal changes (esp. decline in estrogen)
- Confusion in terminology can arise after gynecologic surgery
- Bilateral oophorectomy results in abrupt loss of ovarian function
- Hysterectomy results in cessation of menses even if ovaries remain

Common symptoms of menopause

<table>
<thead>
<tr>
<th>Category</th>
<th>Menstrual changes</th>
<th>Vasomotor symptoms (VMS)</th>
<th>Genitourinary atrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time frame</td>
<td>Before FMP</td>
<td>Before &amp; after FMP</td>
<td>After FMP</td>
</tr>
<tr>
<td>Specific issues</td>
<td>Periods more frequent (&gt;21 days) and/or heavier irregular, infrequent</td>
<td>Hot flashes Night sweats -Sleep disruption -Mood changes -Irritability</td>
<td>Vaginal dryness Dyspareunia Recurrent vaginitis Urinary symptoms -Frequency -Urgency Recurrent UTIs</td>
</tr>
<tr>
<td>Natural History</td>
<td>Ends at FMP</td>
<td>May last for years, but eventually resolve for most women</td>
<td>May present well after FMP Persists &amp; can progress</td>
</tr>
</tbody>
</table>

Case 1: Healthy 45 yo woman bothered by menses getting progressively heavier and often closer together (now every 21-28 days). Full evaluation is normal except for mild anemia.

Which of the following treatments will likely be effective?

A. A. Cyclic progestin (every 3 months)
B. B. Hormone replacement therapy
C. C. Levonorgestrel IUD
D. D. Oral contraceptive
E. E. A and B
F. F. C and D
Duration of VMS: SWAN, 2015

Study of Women’s Health Across the Nation
Observational study of menopausal transition
3302 women at 7 US sites
Subset here =1449 w/ frequent VMS, followed 1996-2013

Median VMS duration 7.4 yrs total (4.5 yrs beyond FMP)
Subgroups:
   Earlier onset in transition: >11.8 yrs total (9.4 yrs post FMP)
   Later onset (after FMP): 3.4 yrs total

Also longer: African-American (10 yrs total); younger age; lower education level; greater perceived stress & symptom sensitivity; higher anxiety/depression scores at onset

Avis et al: Duration of Menopausal Vasomotor Symptoms Over the Menopause Transition. JAMA Internal Medicine Epub 2/16/2015

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Case 2: 50 yo woman presents with hot flashes & night sweats, requesting treatment. Menses have occurred every 2-4 months over the past year.

Which of the following additional history is important to guide discussion of therapeutic options with her?

A. A. Frequency and severity of symptoms
B. B. Her preferences for treatment approaches
C. C. Risk factors affecting treatment options
D. D. All of the above
E. E. No additional history is needed

---

Treatments for VMS

<table>
<thead>
<tr>
<th>Approach</th>
<th>Benefits</th>
<th>Drawbacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle</td>
<td>VMS will resolve eventually in most women</td>
<td>Less effective</td>
</tr>
<tr>
<td></td>
<td>Low cost, natural</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Highly patient-driven</td>
<td></td>
</tr>
<tr>
<td>Botanical</td>
<td>Seen as natural</td>
<td>Less effective than HT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risks of phytoestrogens? Liver disease risk BC?</td>
</tr>
<tr>
<td>Non-hormone Rx</td>
<td>No increase in VTE risk</td>
<td>Less effective than HT</td>
</tr>
<tr>
<td></td>
<td>Less to no increase in breast cancer risk</td>
<td></td>
</tr>
<tr>
<td>Hormone therapy (HT)</td>
<td>Most effective Several delivery forms</td>
<td>Most risks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If uterus: endometrial monitoring or protection</td>
</tr>
</tbody>
</table>

“Step therapy” for VMS

- Hormone therapy
- Non-hormone prescription meds
- Botanical therapies
- Lifestyle measures
There’s an app for that!

- MenoPro: App for iPhone/iPad released in 2014
- by North American Menopause Society (NAMS)
- Goal: help individualize treatment based on pt’s preferences & risk factors.
- Pros: Developed by a medical society
- Free, with no ads or industry support
- Assesses menopause status, symptom severity, & risks
- Provides educational info: lifestyle, diet, & behavior modifications
- Includes tables on risks/benefits of medications
- Includes risk calculators
- Limitations: Currently only available for iPhone/iPad
- Text is college-level to graduate school-level

Do you have moderate-to-severe hot flashes and/or night sweats, defined as bothersome enough to interfere with daily activities, worsen quality of life, and/or interrupt sleep?

Do you have moderate-to-severe hot flashes and/or night sweats, defined as bothersome enough to interfere with daily activities, worsen quality of life, and/or interrupt sleep?

Are you interested in considering menopausal hormone therapy (HT) AND free of the conditions (contraindications) mentioned below?

Hormone Therapy contraindications include: unexplained vaginal bleeding; liver disease; blood clots in the legs or lungs; known blood clotting disorder; untreated hypertension; history of breast, endometrial (uterine) cancer, or other estrogen-dependent tumor; known hypersensitivity to HT, or history of heart attack, angina, coronary bypass surgery, angioptathy/stent, stroke, or TIA. Women with one or more 1st degree relatives with breast cancer (BC) or otherwise at increased risk of BC (see Breast Cancer Risk Score at http://www.cancer.gov/bcrisktool) may want to consider non-hormonal therapies.
Recent Cochrane reviews on VMS

- **Exercise (11/2014):** 5 RCTs
  - No difference: exercise vs no exercise, exercise vs yoga
  - 1 study: exercise + soy milk better than (a) soy milk alone or (b) no intervention
  - 1 study: HT more effective than exercise
- **Relaxation (7/2014):** 4 studies, no evidence of benefit
  - (Paced respiration is recommended on the MenoPro app)
- **Acupuncture (7/2013):** Evidence insufficient & low quality
  - Acupuncture vs no treatment: acupuncture appears beneficial
  - Acupuncture vs sham: no benefit
  - Acupuncture vs HT; acupuncture less effective

Botanicals

- **Black cohosh:** Evidence for efficacy in some trials
  - Does not seem to be a phytoestrogen
  - Binds serotonin receptors (5-HT₁A, 5-HT₁D, and 5-HT₇) (which may be mechanism)
  - Multiple case reports of liver failure
- **Soy isoflavones, genistein:** Evidence for efficacy
  - Studies differ on effect on breast cancer cells
  - Multiple others claimed to help (red clover, linseed, etc)
  - Insufficient evidence and/or no benefit demonstrated

Non-hormonal Rx*

<table>
<thead>
<tr>
<th>Medication</th>
<th>Typical dose used in studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venlafaxine</td>
<td>37.5 – 75mg daily (XR)</td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>50, 100, &amp; 150 mg daily</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>7.5mg capsule, or 12.5-25mg daily (CR)</td>
</tr>
<tr>
<td>Citalopram, escitalopram</td>
<td>10 - 20mg daily</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>15 - 30 mg QHS</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>600 mg QHS, or 300 mg TID, or 1800-2400 mg/day in divided doses</td>
</tr>
<tr>
<td>Clonidine</td>
<td>0.025 – 0.2 mg BID (oral) or 0.1 mg transdermal patch weekly</td>
</tr>
</tbody>
</table>

*All off-label except Brisdelle® (paroxetine 7.5 mg capsule) - the only FDA-approved non-hormone for moderate-severe VMS

Systemic estrogen types, routes

- **Oral**
  - Estradiol
  - Conjugated estrogens
  - Esterified estrogens
- **Transdermal (all estradiol)**
  - Patch
  - Emulsion
  - Gel
  - Spray
- **Transmucosal (ring) (estradiol)**
- **Injection**
Forms of systemic estrogen for VMS (or osteoporosis prevention)

<table>
<thead>
<tr>
<th>Form</th>
<th>Generic</th>
<th>Brand</th>
<th>Cost, $/mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral - estradiol</td>
<td>Yes</td>
<td>Estrace (generic)</td>
<td>10</td>
</tr>
<tr>
<td>Oral – esterified estrogen</td>
<td>No</td>
<td>Menest</td>
<td>45-90</td>
</tr>
<tr>
<td>Oral - estropipate</td>
<td>No</td>
<td>Ogen</td>
<td></td>
</tr>
<tr>
<td>Oral - CEE</td>
<td>No</td>
<td>Premarin, Prempro</td>
<td>140</td>
</tr>
<tr>
<td>Transdermal - patch</td>
<td>Yes</td>
<td>(several)</td>
<td></td>
</tr>
<tr>
<td>Transdermal - emulsion</td>
<td>No</td>
<td>Estrasorb</td>
<td></td>
</tr>
<tr>
<td>Transdermal - gel</td>
<td>No</td>
<td>Divigel, Elestrin, Estragel</td>
<td>100 &amp; up</td>
</tr>
<tr>
<td>Transdermal - spray</td>
<td>No</td>
<td>Evamist</td>
<td>115 &amp; up</td>
</tr>
<tr>
<td>Transmucosal - ring</td>
<td>No</td>
<td>Femring</td>
<td>110</td>
</tr>
</tbody>
</table>

Major risks of hormone therapy (HT)

- Ischemic cardiac disease & dementia: HT raises risk in RCTs of postmenopausal women; emerging “timing hypothesis” for heart and “critical window” for dementia
- Stroke – oral estrogen raises risk, transdermal less so
- VTE risk – oral estrogen raises risk, transdermal less so
- Breast cancer – increases with duration of use (5 yrs)
  - higher with concomitant progestin use
- Endometrial cancer – but progestin protects endometrium

To also consider: ovarian cancer

- Meta-analysis of 53 prospective studies
- 12.1K women developed ovarian cancer
- 55% had been on HT (“use” below)
  - RR 1.25 for long-term use stopped >10 yrs before Dx
  - RR 1.37 for any duration use, stopped <5 yrs before Dx
  - RR 1.43 for current use, even <5 yrs
- If causal, “women who use hormone therapy for 5 years from around age 50 years have about one extra ovarian cancer per 1000 users and, if its prognosis is typical, about one extra ovarian cancer death per 1700 users.”

- Collaborative Group on Epidemiologic Study of Ovarian Cancer
- Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies. Lancet 2/2015 Epub

Duavee®: conjugated estrogens /bazedoxifene

Conjugated estrogens 0.45 mg + bazedoxifene 20 mg 1st TSEC (tissue selective estrogen complex) on market

Bazedoxifene, a SERM protects endometrium & breast
Effect on mammographic breast density = that of placebo

FDA-approved 10/2013 for
- moderate-to-severe hot flashes related to menopause in women who haven’t had a hysterectomy
- prevention of postmenopausal osteoporosis

Duavee®:

- RR 1.25 for long-term use stopped >10 yrs before Dx
- RR 1.37 for any duration use, stopped <5 yrs before Dx
- RR 1.43 for current use, even <5 yrs

$150/mo
### Common symptoms of menopause

<table>
<thead>
<tr>
<th>Category</th>
<th>Menstrual changes</th>
<th>Vasomotor symptoms (VMS)</th>
<th>Genitourinary atrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time frame</td>
<td>Before FMP</td>
<td>Before &amp; after FMP</td>
<td>After FMP</td>
</tr>
<tr>
<td>Specific issues</td>
<td>Periods more frequent (&gt;21 days) and/or heavier</td>
<td>Hot flashes Night sweats Sleep disruption Mood changes Irritability</td>
<td>Vaginal dryness Dyspareunia Recurrent vaginitis Urinary symptoms Frequency Urgency Recurrent UTIs</td>
</tr>
<tr>
<td>Natural History</td>
<td>Ends at FMP</td>
<td>May last for years, but eventually resolve for most women</td>
<td>May present well after FMP Persists &amp; can progress</td>
</tr>
</tbody>
</table>

**Case 3**: Healthy 58 yo woman presents with vaginal dryness and dyspareunia. She tried OTC personal lubricant without benefit. She has seen ads for “the only FDA-approved, non-estrogen, oral pill for moderate to severe painful sex due to menopause” and is interested in trying it. You haven’t heard of it.

- **How would you respond to the patient?**
  - A. How could that even work?
  - B. Sure, I’ll prescribe it. What did you say it was called?
  - C. Let’s look up some information about it, see how it compares to vaginal estrogen, then decide together.
  - D. Here’s a referral to a gynecologist.

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### Osphena®: ospemifene

- **Dose**: 60 mg by mouth once daily
- **Cost**: $200/month
- Osphil:p, a SERM, has a pro-estrogen effect on genitourinary tissue - but in studies up to 1 yr, no effect on endometrium and no observed adverse breast effects
- FDA-approved 2/2013 “to treat women experiencing moderate to severe dyspareunia...a symptom of vulvar and vaginal atrophy due to menopause”
- Stroke & DVT occurred at higher rates than placebo in trials. Labeling, similar to estrogen, warns of possible risk of stroke, clot, breast or uterine cancer & not to use if history of these, or history of heart or severe liver disease

### Vaginal estrogen

- For GU symptoms, all vaginal estrogens are as effective as (a) systemic estrogen and (b) each other...no head-to-head comparison with ospemifene, though
- Vaginal estrogen reduces urinary symptoms including urgency, nocturia, stress incontinence, and frequent UTI (but daily nitrofurantoin is more effective for latter)
- Vaginal estrogens don’t raise systemic levels except at highest dose of cream in FDA labeling (>2 gm/day)
- Endometrial hyperplasia occurred in <0.2% in studies but most lasted 3-12 months & few included biopsies
Topical estrogen for GU atrophy

<table>
<thead>
<tr>
<th>Form</th>
<th>Brand, Dosing</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ring - estradiol</td>
<td>Estring 2 mg</td>
<td>$310 (1 ring, 3 mo)</td>
</tr>
<tr>
<td></td>
<td>1 ring q90 days</td>
<td></td>
</tr>
<tr>
<td>Tablet - estradiol</td>
<td>Vagifem 10 mcg 1 tablet 2x/wk</td>
<td>$400 (24 tabs, 12 wks)</td>
</tr>
<tr>
<td>Cream – estradiol</td>
<td>Estrace 0.1 mg/gm 1-2 gm 1-3x/wk</td>
<td>$240 (42.5 gm, 7-40 wks)</td>
</tr>
<tr>
<td>Cream – conjugated estrogens</td>
<td>Premarin 0.625 mg/gm 0.5 gm 2x/wk</td>
<td>$290 (30 gm, 30 wks)</td>
</tr>
</tbody>
</table>

Cream doses given above are lowest in package inserts, but practitioners commonly advise smaller quantity per dose

Key tips

- For most women, vasomotor symptoms eventually stop (though may last for years)
- Genitourinary symptoms & bone loss continue long-term
- HT is not the only option; it is the most effective but also (in systemic use) poses the most risks
- Medication used for VMS or GU symptoms should ideally be: lowest dose of safest treatment likely to work, targeted to GU tissue if that’s the indication
- If prescribing estrogen for VMS: consider transdermal (less increase in risk of stroke & VTE than oral) and consider generic, whether oral or patch (reduces costs)
Abnormal Uterine Bleeding in Reproductive-Aged Women

Carolyn Gardella, MD, MPH
Associate Professor, UW Dept Ob/Gyn
Women’s Health CME 2015

Objectives
Definition and Nomenclature
Pathophysiology
Age-Based Differential Diagnosis
History, Physical, Labs
Clinical Considerations and Recommendations

What’s Abnormal?

• Abnormal Menstrual Bleeding (AUB) = deviation from the normal cycle length, amount or duration
• 5 days every 21-35 days
• Heavy Menstrual bleeding - >100cc
• Quantification difficult....
  – Bleeding through clothing?
  – Number of tampons or pads per day

Global Nomenclature
International Federation of Gynecology and Obstetrics
Standardized Terminology based on Etiology and Bleeding Pattern
Formerly Known as….

- DUB ➔ Abnormal Uterine Bleeding (AUB)
- Menorrhagia ➔ Heavy Menstrual Bleeding
- Metrorrhagia ➔ Intermenstrual Bleeding

"PALM-COEIN"

**PALM: Structural Causes**
- Polyp
- Adenomyosis
- Leiomyoma
- Malignancy & Hyperplasia

**COEIN: Non-Structural Causes**
- Coagulopathy
- Ovulatory dysfunction
- Endometrial
- Iatrogenic
- Not yet classified

Age-Based Differential Dx

<table>
<thead>
<tr>
<th>13-18 Years</th>
<th>19-39 Years</th>
<th>40 Years to Womenopause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anovulation</td>
<td>Pregnancy</td>
<td>Anovulation</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>Leiomyomas</td>
<td>Endometrial hyperplasia</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Polyps</td>
<td>Polyp</td>
</tr>
<tr>
<td>Pelvic Infection</td>
<td>Anovulatory cycles</td>
<td>Leiomyoma</td>
</tr>
<tr>
<td>Hormonal contraception</td>
<td>Endometrial hyperplasia</td>
<td></td>
</tr>
</tbody>
</table>

A. Hiller-Sturmhefer et al., 1998
Menstrual Symphony

Endometrial Hyperplasia

- Result of unopposed estrogen stimulation of the endometrium
  - Anovulation
    - PCOS, Age
  - Obesity
  - Iatrogenic

Evaluation

- History, detailed
- Exam
- Pregnancy test
- Lab tests - CBC, coags, TSH, LFTs, Fibrinogen, VWF, FSH, Prolactin
- US – TVUS vs. Saline infusion
- Endometrial biopsy
- Hysteroscopy
- D&C
Case 1: Early Reproductive Age

CC: 13 y/o with heavy menses every 6-12 wks
HPI: Soaking through pads and underwear at night
No ER visits for this
Menarche: 12
Not sexually active
No medications
No change in weight

Age-Based Differential Dx

• Anovulation (AUB-O) due to hypothalamic immaturity
  – 70% are regular by 3rd year of menses
  – Anorexia, bulimia
• Coagulopathy
  – 25% of girls with Hct <30%
  – 20-40% of hospitalized girls
  – VonWillebrand most common
• Pregnancy, sexual trauma, STI
• Tumors: Embryonal tumor, choriocarcinoma, polyembryoma, sex cord stromal tumors

Cases – Mid-Reproductive Age

• 24 y/o with menses q 2-3 months, inter-menstrual bleeding and times of heavy menstrual bleeding

• 38 y/o 2 weeks after a D&C for a missed AB with persistent heavy bleeding since the procedure

Mid-Reproductive Age

• Ovulatory dysfunction/PCOS
• Functional
  – Coagulopathy, hypothyroid
• Iatrogenic
  – Anticoagulation, hormonal contraception, hemodialysis
• Pregnancy related
  – SAB, retained products
• Structural
  – Fibroids, polyps, hyperplasia, neoplasia, infection
Case 3: Late Reproductive Age
49 y/o with menses every 10-50 days, intermittently heavy or light, lasting 2-14 days. Also with post coital spotting
BMI: 35
Diabetes
Synthroid, Metformin

To EMB or Not to EMB....
To rule out hyperplasia or cancer
Older than age 45
Or any patient with:
Unopposed estrogen
Failed medical management
Persistent AUB

Imaging

Imaging-MRI
Hysteroscopy

- Goals
  - Control acute bleeding
  - Prevent future bleeding
  - Provide contraception if desired
  - Prevent complications
    - Anemia
    - Hyperplasia/malignancy
    - Surgical intervention

AUB-O (Ovulatory Dysfunction)
- Most common cause
- Non-Acute
- Medical Treatment
  - NSAIDS
  - OCPs (cyclic or continuous)
  - Oral Progestin (cyclic or continuous)
  - Progesterone IUD
  - Anti-fibrinolytics - Tranexamic Acid
  - GnRH Agonists/Antagonists
**NSAIDS**

- More effective than placebo
- Less effective than tranexamic acid or LNG-IUD
- Mefenamic Acid may have less GI effects than ibuprofen/naprosyn

*Duckett and Farquhar Cochrane 2013*

---

**TRANEXAMIC ACID**

- More effective than placebo
- Less effective than tranexamic acid or LNG-IUD
- Mefenamic Acid may have less GI effects than ibuprofen/naprosyn

*Lethaby, Farquhar and Cooke Cochrane Review 2010*

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**OCP vs. PLACEBO**

*Fig. 3. Median menstrual blood loss volume by cycle with extended EE2 valerate and demegest and placebo: intention-to-treat population. For comparative purposes, baseline was calculated as menstrual blood loss volume during the 90-day run-in period multiplied by 0.31 (i.e., 28/90). P<0.05 for reduction in menstrual blood loss volume between non and efficacy periods. In the first cycle of treatment, the first dose of EE2 valerate and demegest and placebo was taken on the first day of menstrual bleeding. Irvine, Enrokat V, and Demegest for Menstrual Bleeding. Obstet Gynecol* 2011

---

**LEVONORGESTREL IUD**

- LNG-IUD vs. Low Dose OCP
  - Reduction in MBL 87.4% vs. 34.9%
- LNG-IUD vs. Extended Progestin
  - Reduction in MBL 94% vs. 87%
  - Satisfaction 76% vs. 22%

Treatment - Surgical

- Dilation and Curettage
- Endometrial ablation
- Hysteroscopic resection of lesions
- Hysterectomy
**AUB-O Acute Bleeding**

- **IV Premarin**
  - 25mg IV q 4-6 hours until slows
  - After acute episode consider 7-10 days progesterone for withdrawal bleed

- **IV Tranexamic Acid**
  - 1mg/kg q 8 hours

- **Amicar**
  - 4-5 gram IV load then 1 gram/hour

---

**Case - Postmenopause**

59 y/o underwent menopause at age 51 with new onset bleeding - light bleeding for 4 days, now stopped
Postmenopausal

- Cancer - 10%
- Structural cause - 80%
  - Polyps, submucosal myoma
- Hyperplasia
- Atrophy
- HRT related

CONCLUSIONS

- PALM-COEIN is a useful tool to describe abnormal uterine bleeding
- Utilize individualized medical therapy to stop current bleeding and prevent future bleeding
- In acute heavy bleeding, assess stability and consider the OR in unstable patients

Algorithm References

- Munro MG. FIGO Classification system (PALM-COEIN for causes of abnormal uterine bleeding in nongravid women of reproductive age. JOG 2011 April;113(1):3-13