Evaluation & Management of Overactive Bladder

Michael Fialkow, MD MPH
Urogynecology (FePMRS)
mfialkow@uw.edu

Disclosures/Conflict of Interest/Bias

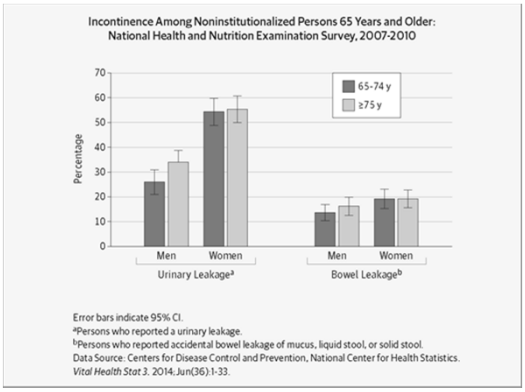
- I have no financial relationship with any of the companies that produce the products I'm about to discuss
- I have no conflicts of interest.
- I specifically **don't encourage OR discourage** use of any particular product

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?

US Toll From Incontinence
JAMA. 2014;312(9):884.



Incontinence among noninstitutionalized persons aged 65 and over, by age and sex: National Health and Nutrition Examination Survey, 2007–2010

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° - <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

International Continence Society, 2nd Intnl. Consultation on Incontinence, 2002

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° - <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

International Continence Society, 2nd Intnl. Consultation on Incontinence, 2002

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
2cups of coffee daily
No medical problems
PE:"normal" pelvic although leaks a small amount with valsalva
- "weak" pelvic floor contraction

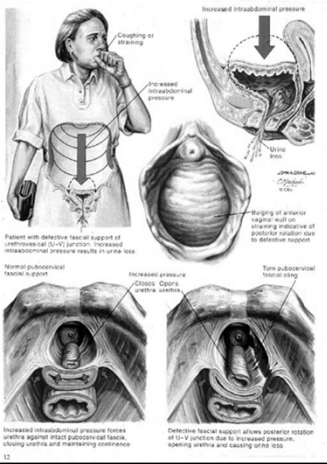
By description does Jane have:

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

Differentiating OAB from SUI

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

Abrams P, Wein AJ. *The Overactive Bladder:* Erik Sparre Medical AB; 1998.



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

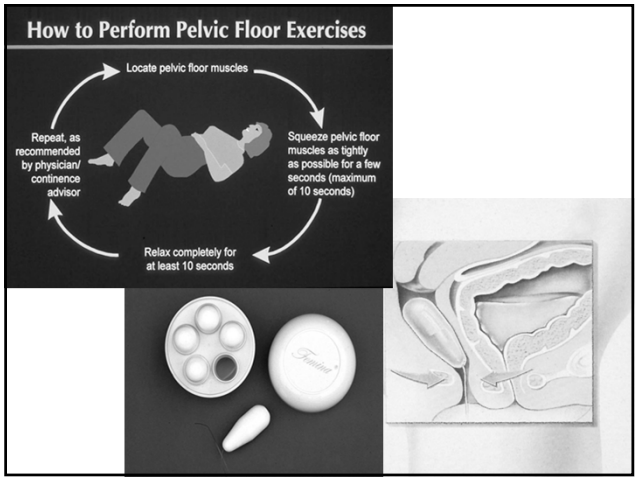
- Alcohol
- Apples
- Aspartame
- Carbonated beverages
- **Citrus Fruit/ Juices**
- Chocolate
- **Coffee (caf or decaf)**
- **Cranberries (+ juice)**
- Grapes
- Guava
- Pineapple
- Strawberries
- Sugar
- Spicy Foods
- **Tea (Black & Green – Not herbal)**
- Tomato-based Foods
- Vitamin B
- Vinegar

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

Fantyl, JAMA 1991; Jarvis, Br. Med J 1980



Carol

74-yo P3 complains of soaking through her pads
- "Can' t reach toilet when I get the urge"
- Has been a problem for "years"

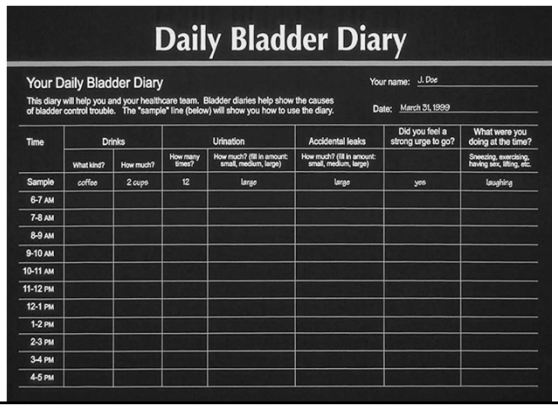
Voids 3 times per night

Drinks 4 cups of coffee per day

Med Hx: Htn

PE:"Moderate"cystocele & "weak" pelvic floor contraction

Quick side note



Daily Bladder Diary

Your Daily Bladder Diary

This diary will help you and your healthcare team. Bladder diaries help show the causes of bladder control trouble. The "sample" line (below) will show you how to use the diary.

Your name: J. Doe

Date: March 31, 1999

Time	Drinks		Urination		Accidental leaks	Did you feel a strong urge to go?	What were you doing at the time?
	What kind?	How much?	How many times?	How much? (fill in amount: small, medium, large)	How much? (fill in amount: small, medium, large)		Sneezing, exercising, having sex, lifting, etc.
Sample	coffee	2 cups	12	large	large	yes	laughing
6-7 AM							
7-8 AM							
8-9 AM							
9-10 AM							
10-11 AM							
11-12 PM							
12-1 PM							
1-2 PM							
2-3 PM							
3-4 PM							
4-5 PM							

Which drug would you offer Carol 1st?

1. Tolterodine (Detrol)
2. Oxybutynin (Ditropan/Generic)
3. Darifenacin (Enablex)
4. Solifenacin (Vesicare)
5. Trospium (Sanctura)
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 24°
- 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

Hay-Smith, J The Cochrane Library 2004

Anti-cholinergics For OAB

Tolterodine (Detrol) IR: 1 - 2 mg BID LA: 2 - 4 mg QD
Trospium (Sanctura) IR: 20 mg BID XR: 60 mg QD
Oxybutynin Chloride (Ditropan) IR: 5 mg BID - TID **Patch: 3.9 mg QD (OTC)** ER: 5/10/15 mg QD
Darifenacin (Enablex): ER: 7.5/15 mg QD
Solifenacin (Vesicare): ER: 5/10 mg QD
Fesoterodine (Toviaz): ER: 4/8 mg QD

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

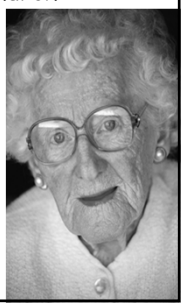
Side effects
Dry mouth, Constipation, Blurred vision, Headace, CNS effects

Generics
- Oxybutynin
- Tolterodine

Alice

83-yo who complains of frequent urination when she is "out and about"
- 1° complaint: Goes too often @ church
- Not bothered @ home or @ night

NO dietary irritants except 1g tea
Med Hx: Htn, Glaucoma
PE: Pelvic floor strength is poor
Significant atrophy (PMP since 50)



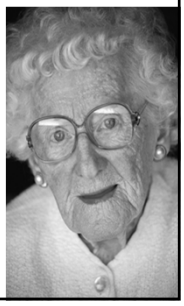
Which drug would you offer Alice?

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

Alice

83-yo who complains of frequent urination when she is "out and about"
- **1° 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)



Anti-cholinergics For OAB

Tolterodine (Detrol) **IR: 1 - 2 mg BID** LA: 2 - 4 mg QD
Trospium (Sanctura) **IR: 20 mg BID** XR: 60 mg QD
Oxybutynin Chloride (Ditropan) **IR: 5 mg BID - TID** Patch: 3.9 mg QD (OTC) ER: 5/10/15 mg QD
Darifenacin (Enablex): ER: 7.5/15 mg QD
Solifenacin (Vesicare): ER: 5/10 mg QD
Fesoterodine (Toviaz): ER: 4/8 mg QD

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

Side effects

Dry mouth, Constipation, Blurred vision, Headace, CNS effects

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

Estrogen & OAB

	Oxybutynin			Estradiol ring			
	Baseline	12 wk	*P*	Baseline	12 wk	*P*	Difference between groups
No. of voids in 24 h	14.7 (5.3)	11.7 (6.1)	0.003	14.9 (5.3)	10.4 (4.2)	<0.001	0.71
UDI-6 score	12.1 (4.3)	9.4 (4.8)	0.003	11.4 (3.5)	7.8 (4.3)	<0.001	0.58
IIQ-7 score	14.7 (5.8)	11.3 (6.9)	0.02	13.2 (4.8)	8.1 (6.4)	<0.001	0.37
Vaginal pH level	5.8 (0.9)	5.8 (0.8)	0.72	6.0 (1.0)	4.9 (0.9)	0.002	<0.001
Maturation index	36.3 (34.4)	34.8 (30.1)	0.76	24.3 (28.3)	70.1 (21.5)	<0.001	<0.001

Data are presented as mean (SD).
UDI, Urogenital Distress Inventory; IIQ, Incontinence Impact Questionnaire.

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

Nelken. Menopause. 2011

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

has tried 3 different meds

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?

Depression and UI

TABLE 2 -- Adjusted odds of incident UI [a]

Predictors (baseline)	Adjusted OR [b] (95% CI)
Major depression (CIDI-SF)	1.46 (1.08–1.97)
BMI [c]	
25-29 (overweight)	1.41 (1.15–1.73)
≥30 (obese)	1.43 (1.14–1.80)
Parity [d]	
1-2 deliveries	1.11 (0.78–1.58)
≥3 deliveries	1.43 (1.02–2.00)

TABLE 3 -- Adjusted odds of probable major depression (CES-D ≥6) [a]

Predictors (baseline)	Adjusted OR [b] (95% CI)
Incontinence	1.03 (0.75–1.42)
BMI [c]	
25-29 (overweight)	1.15 (0.87–1.53)
≥30 (obese)	1.46 (1.08–1.98)
Medical comorbidity [d]	
Mild	1.65 (1.15–2.36)
Moderate-severe	1.74 (1.11–2.74)

Melville et. al. Am J Obstet Gynecol. 2009 Nov;201(5) Epub 2009 Aug 29

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

Should we offer her the usual?

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

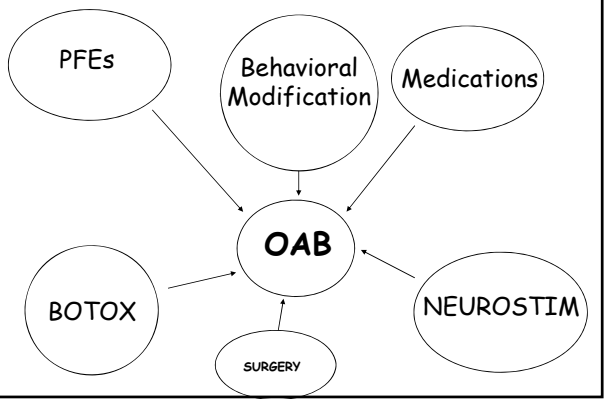
3 Options for 2nd Line Management

- 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
    - Nocturia (Imipramine)
  - Vaginal estrogen effective in atrophic PMP women
- If unimproved/symptom confusion:
  - Diary
  - Consider Depression/other meds
- If nothing works consider referral
  - Neuromodulation or Botox

OAB Management Overview



RECURRENT URINARY TRACT INFECTIONS

Anna C. Kirby, MD, MAS
Acting Assistant Professor
University of Washington
Division of Urogynecology
Department of Obstetrics and Gynecology
March 27, 2015

DISCLOSURES

- No financial relationships to disclose.

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

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

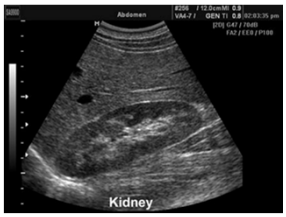
Why is she having rUTIs?

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

empowher.com

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)



geocities.ws

Prevention

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

oxygenpharmacy.com

Prevention

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

cnn.com

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

Regimens	Expected UTIs per year
Trimethoprim-sulfamethoxazole 40 mg/200 mg	0.30
Trimethoprim-sulfamethoxazole 80 mg/400 mg	0.00
Nitrofurantoin 50 mg or 100 mg	0.10
Cephalexin 250 mg	0.03
Ciprofloxacin 125 mg	0.00
Norfloxacin 200 mg	0.00
Ofloxacin 100 mg	0.06

UpToDate®

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

playbuzz.com

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?

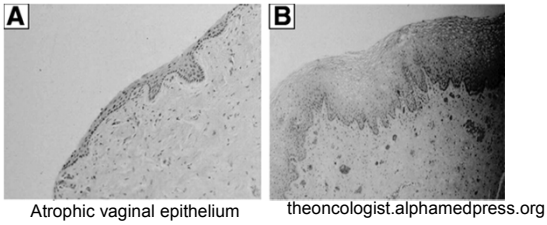
- Menopause.

womenofgrace.com

- 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

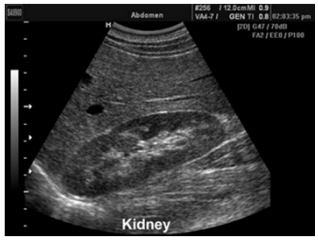


Atrophic vaginal epithelium

theoncologist.alphamedpress.org

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 lactobacillis -> reduce colonization of harmful bacteria
- Note: Warn her about the warnings!
  - Same as oral HRT but low systemic absorption, so only small, theoretical risk

articles.philly.com

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

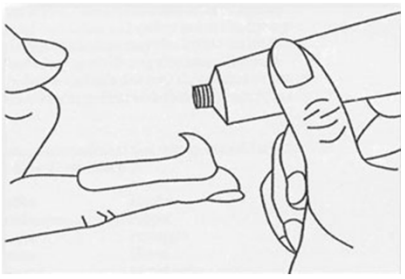
Estradiol 10mcg tablets (Vagifem)

- one tab 2 nights per week

Estradiol 2mg ring

- one ring every 3 months

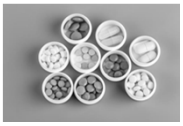
(*throw away the applicators*)



urologyteam.com

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



healthtap.com

Goal: 6 months no UTIs

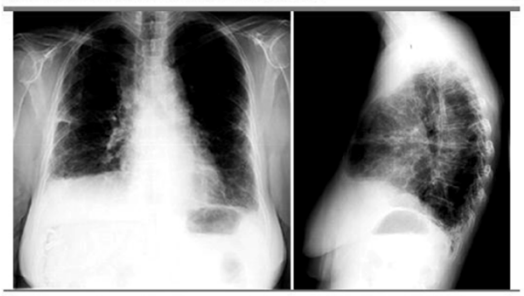
Continuous antimicrobial prophylaxis regimens for women with recurrent urinary tract infection

Regimens	Expected UTIs per year
Trimethoprim-sulfamethoxazole 40 mg/200 mg once daily	0 to 0.2
Trimethoprim-sulfamethoxazole 40 mg/200 mg thrice wkly	0.1
Trimethoprim 100 mg once daily	0 to 1.5*
Nitrofurantoin 50 mg once daily	0 to 0.6
Nitrofurantoin 100 mg once daily	0 to 0.7
Cefaclor 250 mg once daily	0
Cephalexin 125 mg once daily	0.1
Cephalexin 250 mg once daily	0.2
Norfloxacin 200 mg once daily	0
Ciprofloxacin 125 mg once daily	0

* High recurrence rates observed with trimethoprim associated with trimethoprim-resistance.

UpToDate®

Nitrofurantoin-induced pulmonary injury



Posteroanterior and lateral chest radiographs show bilateral pleural effusions and parenchymal changes, predominantly located in the lower zones, in a 69-year-old woman who received nitrofurantoin for ten years because of recurrent urinary tract infections. Her symptoms consisted of dyspnea and a dry cough.
Courtesy of Justus de Zeeuw, MD

UpToDate

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

Webmedia.unmc.edu

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%

Treat acute UTIs

- 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

nadirkeval.com

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. PMH: diabetes. PSH: none.
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.

papaswords.com

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

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

Wolfe F, et al. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 1995;38:19-28.

Haskell SG, et al. Prevalence of painful musculoskeletal conditions in female and male veterans in 7 years after return from deployment in Operation Enduring Freedom/Operation Iraqi Freedom. Clin J Pain 2012;28(2):163-167.

Stubbs D, et al. Sex differences in pain and pain-related disability among primary care patients with chronic musculoskeletal pain. Pain Med 2010;11:232-329

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

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 – wt gain
2. Venlafaxine – liver disease
3. Desipramine – sedating TCA, no wt gain
4. Gabapentin – wt gain
5. Amitriptyline – OK, but likely wt gain

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

Atkinson JH, et al. Efficacy of noradrenergic and serotonergic antidepressants in chronic back pain: a preliminary concentration-controlled trial. J Clin Psychopharmacol 2007;27(2):135–142.

Tricyclics

- Amitriptyline → nortriptyline
- Imipramine → desipramine

TCA	Anticholinergic	Drowsiness	Weight Gain	Sexual Dysfunction
Amitriptyline	4+	4+	4+	3-4+
Nortriptyline	2+	2+	1+	unknown
Imipramine	3+	3+	4+	3+
Desipramine	1+	4+	1+	unknown

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

Saarto T et al. Cochrane 2007.

Tricyclics

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

DeVane CL. Pharmacogenetics and drug metabolism of newer antidepressant agents. J Clin Psychiatry. 1994;55(suppl):38–45. discussion 46–7.

Spina E et al. Relationship between plasma desipramine levels, CYP2D6 phenotype and clinical response to desipramine: a prospective study. Eur J Clin Pharmacol 1997;51:395-398.

Gardiner SJ, Begg EJ. Pharmacogenetics, drug-metabolizing enzymes, and clinical practice. 2006;58(3):521-590.

J Kirchheiner et al. CYP2D6 and CYP2C19 genotype-based dose recommendations for antidepressants: a first step towards subpopulation-specific dosages. Acta Psychiatrica Scandinavica. 2001;104(3):173-192

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	Levothyroxine
Sertraline 200mg	Lisinopril
Carisoprodol	Metoclopramide
Clonazepam	Methadone 15mg TID
Cyclobenzaprine	Risperidone 2mg QHS
Etodolac	Zolmitriptan prn

Case #2:

What else is going on?

Amitriptyline 200mg	Levothyroxine
Sertraline 200mg	Lisinopril
Carisoprodol	Metoclopramide
Clonazepam	Methadone 15mg TID
Cyclobenzaprine	Risperidone 2mg QHS
Etodolac	Zolmitriptan prn

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
2. Venlafaxine
3. Gabapentin
4. Duloxetine
5. Pregabalin

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

Medication	Dose	Cost per month
Acetaminophen	1000mg TID	$4
Naproxen	440mg BID	$8
Desipramine	25mg QHS	$30
Nortriptyline	25mg QHS	$14
Gabapentin	600mg TID	$25
Pregabalin	150mg BID	$300
Venlafaxine	150mg BID	$40
Desvenlafaxine	100mg BID	$250
Duloxetine	60mg Daily	$50
Milnacipran	50mg BID	$126

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

Mason BJ. Gabapentin treatment for alcohol dependence: A randomized controlled clinical trial. JAMA Int Med 2014;174(1):70-77.

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

Arnold LM et al. Gabapentin in the treatment of fibromyalgia. Arthritis & Rheumatism 2007:56(4);1336-1344.

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 f/u 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 the10-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

Kalita J et al. An open labeled randomized controlled trail of pregabalin versus amitriptyline in chronic low backache. Journal of the Neurological Sciences 2014.;342:127-132

Amitriptyline vs. pregabalin:

Results after 14 weeks:

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

- 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

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
  - Increase BP (venlafaxine)
  - Withdrawal 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

- Norepinephine > 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)

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~~ → incr TCA levels
- ~~TCA + venlafaxine~~ → QT prolongation

Gilron I, et al. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised controlled crossover trial. Lancet. 2009;374:1252–1261.

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

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

Med	Start dose	Max dose	Pros	Cons	Comments
Tylenol	Any	1000mg/dose, 3000mg/day	No GI upset, non-sedating	Liver toxicity with overdose	Counsel re: overdose
NSAIDs	Any	Naproxen: 500mg bid Ibuprofen: 800mg tid	Non-sedating	Kidney and GI risk, unsafe in cardiac disease.	UpToDate table - nuances
TCAs	10mg qhs	Usually 50mg for chronic pain. Up to 100-150mg used for depression.	Help sleep, avoid weight gain.	Dry mouth, constipation, sedation. Unsafe if CVD/CVA. Serotonin syndrome.	Amitriptyline more sedating, more anticholinergic.
Gabapentin	300mg daily (100mg if very med-sensitive)	1200mg tid	Oldie/goodie. Does not interact with MH meds, generally a mood stabilizer.	Sedation, dizziness, wt gain. No abrupt stop. Long titration, many pills.	Good combo with TCA or venlafaxine. Renal dz: reduce.
Pregabalin	150mg total (75mg bid)	450mg total (150mg tid or 225mg bid)	Often better tol. than gabapentin, easier dosing.	Weight gain, sedation.	Expensive
Venlafaxine	37.5mg bid	225mg/day (75mg tid)	No weight gain. Works directly for pain, as well as depression treatment.	GI sx's at start. Incr BP. Withdrawal sx's, taper over several weeks.	Lowers sz threshold.
Duloxetine	30mg daily x one week	60mg daily (up to 120mg for depression)	Also treats depression, no weight gain, no sedation.	GI sx's at initiation (less than venlafaxine). Withdrawal sx's.	Expensive
Milnacipran	12.5mg daily x 1d 12.5mg bid x2d 25mg bid x 4d	Usual: 50mg bid Max: 100mg bid		Renal disease: reduce by 50% if CrCl <30 Liver disease: caution	Expensive
Tramadol	50-100mg q4-6hrs	400mg/day	Not usually sedating, better tolerated than opiates, less addictive (but still potential)	Potential increase suicide risk, and risk of serotonin syndrome if on other serotonergics	Acts like opiate, inhibits serotonin and norepinephrine uptake.

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**

Thank you

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
  - SSRI's: 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

Boyle J, et al. Randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic peripheral neuropathic pain: impact on pain, polysomnographic sleep, daytime functioning, and quality of life. Diabetes Care 2012;35:2451–8.

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

Disclosure

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

Objectives

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

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

Creinin MD, et al. Obstet Gynecol Surv 2001;56:105-13.

EPL Definitions

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

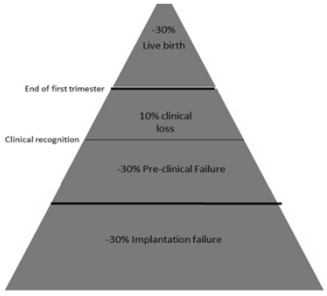
Goldstein SR, et al. Obstet Gynecol 1998;80:670-2

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

TEAMM Training, Education, & Advocacy in Miscarriage Management

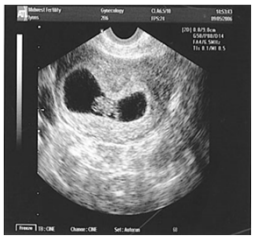
Imperfect obstetrics: most don't continue



Brown S, Miscarriage and its associations. Sem Repro Med.

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.

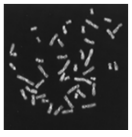


The most likely reason for her EPL is:

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



TEAMM Training, Education, & Advocacy in Miscarriage Management

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

TEAMM Training, Education, & Advocacy in Miscarriage Management

Milestone of embryology as assessed by TVUS

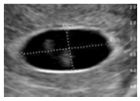
Timing of first appearance of gestational landmarks on transvaginal ultrasound examination

Landmark	First appearance on transvaginal ultrasound examination
Gestational sac	4.5 to 5 weeks
Yolk sac	5 weeks
Cardiac activity	5.5 to 6 weeks
Measurable crown-rump length	6 weeks

UpToDate®

U/S Dating in Normal Pregnancy

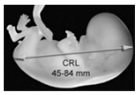
Gestational Age *(days)* =



Mean Sac Diameter *(mm)* + 30

OR

Crown-Rump Length *(mm)* + 42



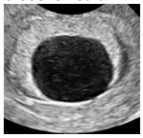
Clinical Presentation of EPL

- Bleeding
- Pain/cramping
- Falling or abnormally rising ßhCG
- Decreased symptoms of pregnancy
- No symptoms at all!

TEAMM Training, Education, & Advocacy in Miscarriage Management

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

Doubilet PM. Diagnostic Criteria for Nonviable Pregnancy Early in the First Trimester. NEJM. Oct. 10, 2013

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

Sotiriadis A, Obstet Gynecol 2005
Nanda K, Cochrane Database Syst Rev 2006

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 2005

Table 4. **Adverse Events and Acceptability of Medical and Surgical Treatment of Early Pregnancy Failure.***

Variable	Misoprostol	Vacuum Aspiration	P Value†
Adverse event			
Hemorrhage requiring hospitalization with or without blood transfusion — % (no./total no.)	1 (5/488)	1 (1/148)	1.0
Hospitalization for endometritis — % (no./total no.)	<1 (2/488)	0 (0/148)	1.0
Fever (temperature ≥38.0°C [100.4°F]) — % (no./total no.)	3 (13/477)	4 (6/148)	0.41
Emergency visit to hospital within 24 hr after treatment — % (no./total no.)	3 (15/488)	2 (3/148)	0.59
Unscheduled hospital visits — % (no. of visits/total no. of patients)‡	23 (114/488)	17 (25/148)	0.09
Change in hemoglobin between day 1 and day 15 — g/dl§	−0.65±1.10	−0.18±0.89	<0.001
Decrease in hemoglobin ≥2 g/dl — % (no./total no.)§	9 (38/421)	4 (5/134)	0.05
Decrease in hemoglobin ≥3 g/dl — % (no./total no.)§	5 (19/421)	1 (1/134)	0.04
Nausea — % (no./total no.)¶	53 (250/472)	29 (41/141)	<0.001
Vomiting — % (no./total no.)¶	20 (96/475)	7 (10/142)	<0.001
Diarrhea — % (no./total no.)¶	24 (113/473)	10 (14/142)	<0.001
Abdominal pain — % (no./total no.)¶	99 (473/476)	95 (134/141)	<0.001
Pain-severity score¶‖	5.7±2.4	3.2±2.4	<0.001
Acceptability — % (no./total no.)			
Would probably or absolutely recommend this procedure	83 (379/456)	83 (125/150)	0.95
Would probably or absolutely use this treatment again	78 (357/456)	75 (112/150)	0.36

Zhang, NEJM 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.

TEAMM Training, Education, & Advocacy in Miscarriage Management

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

TEAMM Training, Education, & Advocacy in Miscarriage Management

Misoprostol

- Prostoglandin 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

Chen B, Clin Obstet Gynecol 2007

Why Misoprostol?

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

Misoprostol Dosing Regimens

Embryonic Demise & Anembryonic Pregnancy

Study	***Dose***	***Efficacy***
Creinin	400 mcg po vs 800 pv	25% vs. 88%
Ngoc	800 mcg po vs 800 pv	89% vs. 93% (NS)
Tang	600 mcg SL vs 600 pv q 3 hrs x 3 doses *(SL had more side effects—diarrhea, 70% vs 27.5%)*	87.5%
Phupong	600 mcg po x 1 vs. q 4 hrs x 2 doses *(Repeat dosing increased diarrhea, 40% vs 18%)*	82% vs 92% (NS)
Gilles	800 mcg pv saline-moistened vs. dry	83% vs 87% (NS)

Creinin MD, Obstet Gynecol 1997; Ngoc NTN, Int.J Gynaecol Obstet 2004; Tang OS, Hum Reproduct 2003; Phupong V, Contraception 2005; Gilles JM, Am J Obstet Gynecol 2004

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%

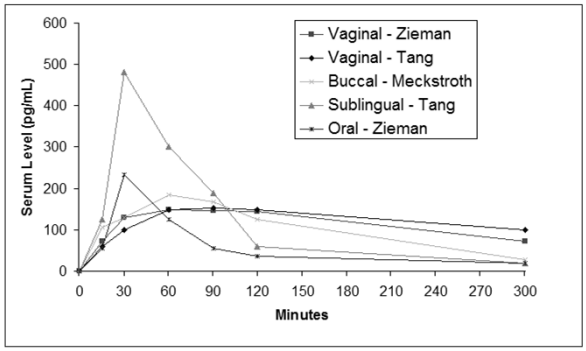
Success rate depends on type of miscarriage

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

Wood SL, Obstet Gynecol 2002; Bagratee JS, Hum Reproduct 2004; Blohm F, BJOG: Int J Obstet Gynecol 2005

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

Wood SL, Obstet Gynecol 2002; Bagratee JS, Hum Reproduct 2004; Blohm F, BJOG: Int J Obstet Gynecol 2005

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

Gronlund A, Acta Obstet Gynaecol 1998; Nielsen S, Br J Obstet Gynaecol 1997; Niinimaki M, Fertility Sterility 2006; Schreiber CA, Contraception 2006

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

Creinin MD, Contraception 1993

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 B, Contraception 2001
Reynolds A, Eur. J Obstet Gynecol Reproduct. Biol 2005

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

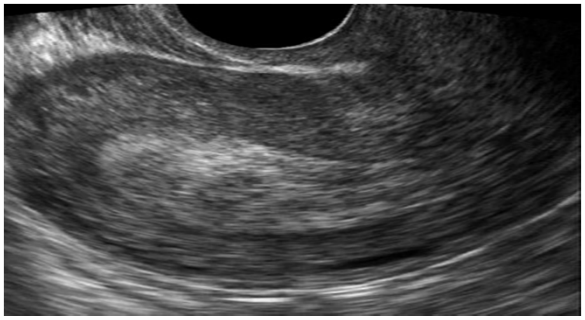
26 yo G2P1, CRL of 7mm but no cardiac activity

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

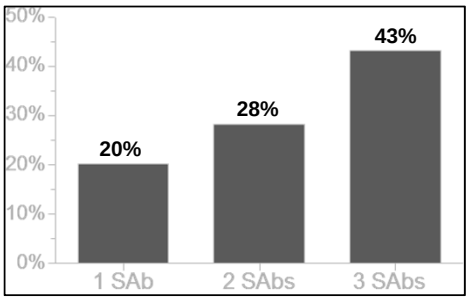
26 yo G2P1, CRL of 7mm but no cardiac activity



Is Samantha's pregnancy loss complete?

1. Yes
2. No

Future Risk of Early Pregnancy Loss



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 ßhCG values after 2–4 weeks
- Appropriate grief counseling

Goldstein R, Am J Obstet. Gynecol 2002; Wyss P, J Perinat Med 1994; Grimes D, Cochrane Database Syst Rev 2000

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

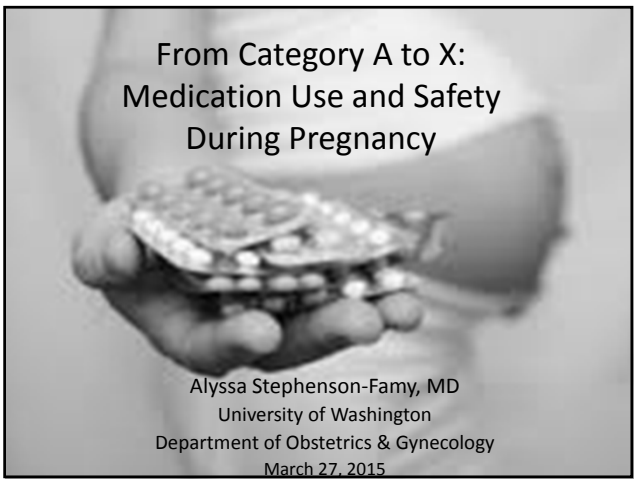
Thanks!

?

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

Disclosures

- No disclosures

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

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
  - Favored 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 – on line
- 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 can not be easily extrapolated to humans
  - Crossing placenta ≠ birth defects!!
  - Difficult to define drug effects vs. disease effects
- *Tip: Lactmed – (lactation) download the app!*

+ LactMed

iTunes free iPhone app

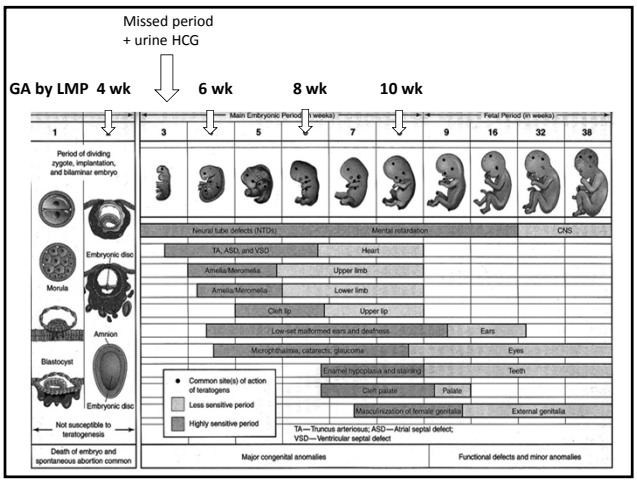
Google for android app

http://toxnet.nlm.nih.gov

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

HgbA1c (%)	Fetal anomalies (%)	Relative Risk
<9.3%	3	1
9.4-11	6	2
11-12.7	8	2.5
12.8-14.4	33	10.7
>14.4	40	13.4

Teratogenic: Maternal Diabetes

Fetal Anomaly	Embryonic Age	Incidence
Caudal regression	>3 weeks	200X
Spina bifida	4 weeks	10X
Situs inversus	4 weeks	40X
Cardiac	5-6 weeks	
Renal	5 weeks	
Anal/rectal atresia	6 weeks	

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

Study	Rad
CXR	0.001
V/Q scan	0.03
DEXA	0.6
Abd CT	0.8
Angiogram	2.5 rad

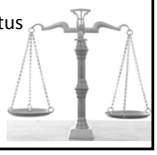
Good news: Dental X-rays are 0 rads!

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)?

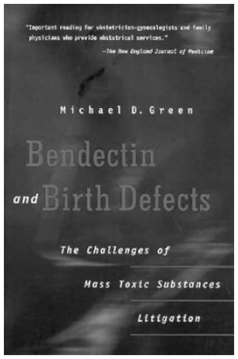
- What is the most famous teratogen?

Thalidomide

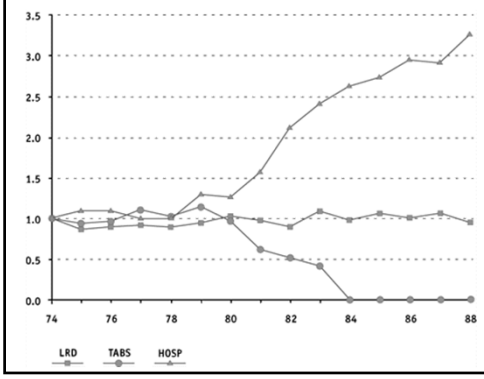
Limb reduction defect: phocomelia

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.

Pregnancy Category	Definition
A	Studies in pregnant women have shown that the medicine does not present an increased risk to the baby.*

* 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, microophthalmia
- Methotrexate
  - Craniofacial, skeletal, cardio-pulmonary and GI, developmental delay, miscarriage
- Accutane (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 (doxycyline): permanent discoloration of teeth, enamel hypoplasia
  - Quinolones (ciprofloxacin, levofloxacin): joint concerns
- Safe:
  - Nitrofurantoin, sulfaonamides → 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

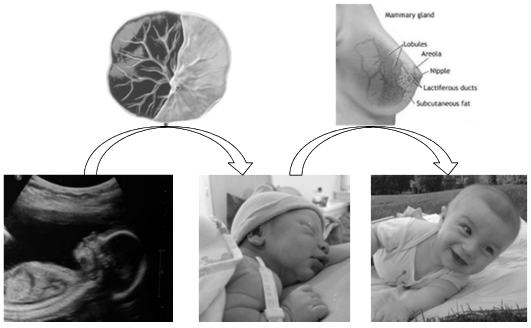
Rheumatologic Medications

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

Rheumatologic Medications

Medication	Category	Risks	Lactation
TNF inhibitors (remicade, enbrel, humira)	B	Possible VACTERL association	Limited data, but no adverse effects
Cyclosporine	C	PTB, LBW observed in transplant	No adverse effects, may follow levels
IVIG	C	Crosses placenta >32 wks	Normal IgG and IgM levels in milk
Tacrolimus	C	No consistent pattern of anomalies	No adverse effects, may follow levels
Cyclophosphamide	D	SAB, teratogenic	Not recommended
Mycophenolate (cellcept)	D	SABs and teratogenic (cleft, limb, heart, renal)	Not recommended
Methotrexate	X	SAB, teratogenic	May follow levels in low dose patients
Rituximab	C	B-cell depletion	Insufficient data

So you are going to continue a medication in pregnancy…



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

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, Psudoephedrine, Primidone, Sulfasalazine,
- ***Drug effect unknown but may be of some concern:***
  - Anxiolytics, some SSRIs and antipsychotics, amiodarone, metronidazole, tinidazole, chloramphenicol, lamotrigine

\+ LactMed

iTunes free iPhone app

Google for android app

http://toxnet.nlm.nih.gov

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

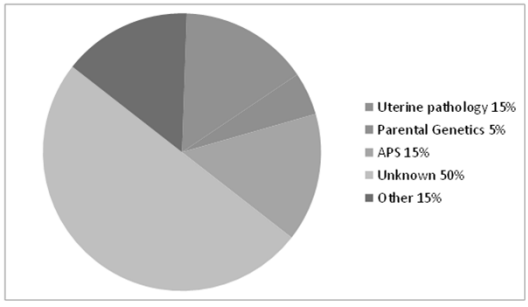
ASRM Committee Opinion, Fertility and Sterility Jan 2012

Question #2

What is the most common cause of miscarriage?

- Blood clotting issue
- Immune issue
- Unexplained
- Uterine issue

Causes of RPL



Other includes: endocrine disorders, obesity

Evaluation of RPL - History

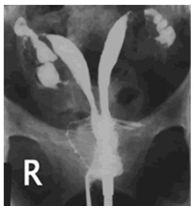
- Thorough history and physical
  - Age, BMI
  - Obstetric history, timing of loss, testing on POC
  - Menstrual cycles
  - Patient and FHx clotting disease
  - Medical history – diabetes, thyroid disease

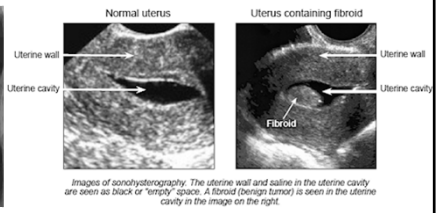
Evaluation of RPL - Testing

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

- What about the other 50%?

Uterine Cavity Evaluation



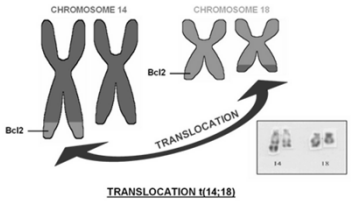


Images of sonohysterography. The uterine wall and saline in the uterine cavity are seen as black or "empty" space. A fibroid (benign tumor) is seen in the uterine cavity in the image on the right.

- Hysteroscopy, Hysterosalpingogram (HSG) or **Saline Infusion Sonogram/sonohystogram**
- Evaluating for congential 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



TRANSLOCATION t(14;18)

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-eclampia, placental insufficiency

Antiphopholipid consensus group. Miyakis S et al. J Thromb Haemost 2006;4:295-306

Antiphopholipid 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

Antiphopholipid consensus group. Miyakis S et al. J Thromb Haemost 2006;4:295-306
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

Testing Not Recommended

- Cultures for bacteria
- Endometrial biopsies for luteal phase defect
- Male factor
- ANA
- HLA typing
- Embryotoxin 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

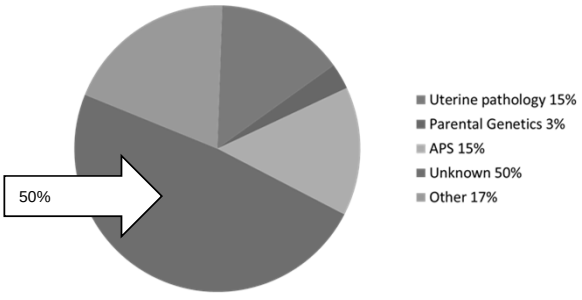
Thrombophilia testing (FVL, prothrombin gene mutation, etc.) is a part of a standard evaluation for RPL?

- 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)

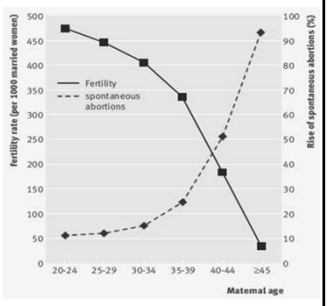
Unexplained RPL



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



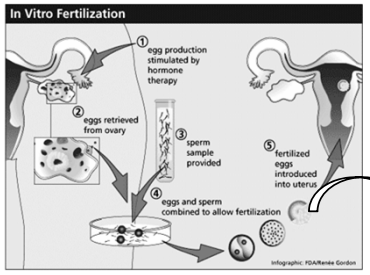
Jacobs 1987, Stevenson 2002, Hassold 1985, Marqard 2010

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



Blastocyst biopsy of 4-5 cells from trophectoderm

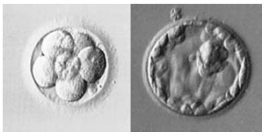
Technology of genetic testing developing

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



Pacific NW Fertility and IVF Specialists

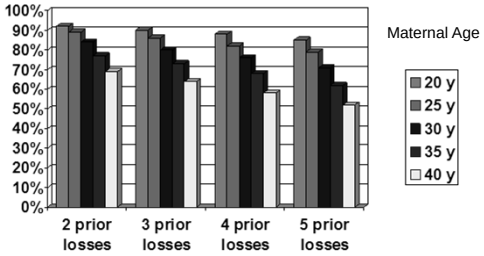
Evidence for IVF/PGS for RPL

- 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% ($P<0.1$)

Pacific NW Fertility and IVF Specialists

Prognosis

Unexplained RPL, No intervention

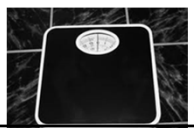


Brigham SA. Hum Rep 1999

Pacific NW Fertility and IVF Specialists

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

Pacific NW Fertility and IVF Specialists

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 Treamtent

- 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

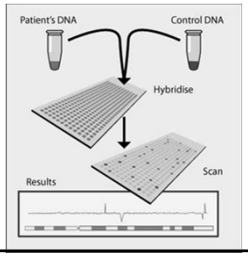
Aneuploidy in POC

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

Pacific NW Fertility
and IVF Specialists

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

Growth

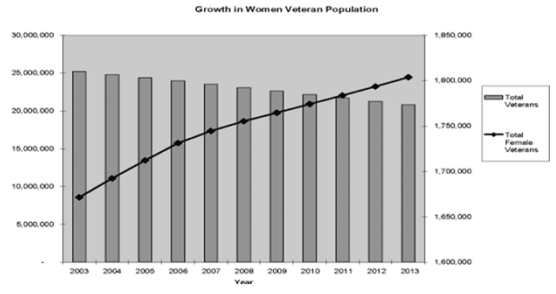
- **Women are the fastest growing segment of the VA population**
  - **15% active soldiers are women**
  - **Number WV expected to double in 5 yrs**
  - **% Women utilizing VA more than men (OIF/OEF)**

- **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)



7

What percentage of Air Force active duty soldiers are women?

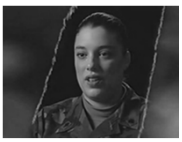
A. **10%**
B. **15%**
C. **18%**
D. **20%**
E. **24%**
F. **28%**

What percentage of Air Force active duty soldiers are women?

A. 10%
B. 15%
C. 18%
D. 20%
E. 24%
F. 28%

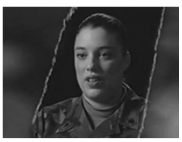
What percentage of Army active duty soldiers are women?

A. 10%
B. 15%
C. 18%
D. 20%
E. 24%
F. 28%



What percentage of Army active duty soldiers are women?

A. 10%
B. 15%
C. 18%
D. 20%
E. 24%
F. 28%



Post-Deployment

A New Generation of Women Veterans

Recognize women veterans' unique and complex health needs

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

WOMEN VETERANS HEALTH CARE

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

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

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

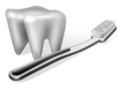
Adjustment reaction	58%
Depressive disorders	47%
Anxiety, adjustment, dissociative, mood, somatoform disorders	36%
Nondependent drug abuse	31%
Affective psychosis	28%

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 stressorsSD**

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

US Military: Women informally In "combat" roles

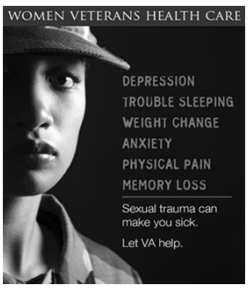
- **In fact women have been/are serving in direct combat ground operations in Iraq and Afghanistan; no "front line"**

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
  - Street, *Clin Psychol Review* 2009; 685-694.
- 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 ***US P.L. 102-585, 1992; 108-422, 2004***

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

	Females	Males
% Screened Positive	20%	1%
# Screened Positive	48,000	44,000

National All Veteran Data FY 2010 (similar 2011-12)

36

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**

46

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

49

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)

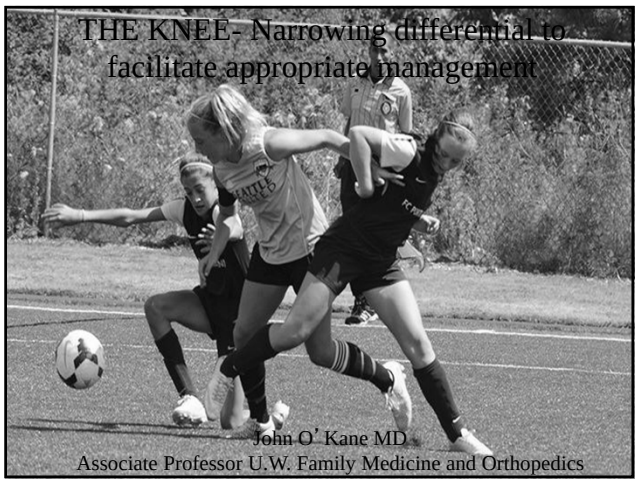
50

"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, resiliant, and keep trying to get help and move forward!"

Thank you

Additional References – 1

- Levander X, Overland S. Care of Women Veterans. *Med Clin North Am*. In Press 2015.
- Murdoch M, et al. Women and war: what physicians should know. *J Gen Intern Med*. 2006; 21:S5–10.
- Armstrong K, et al. *Courage After Fire: Coping Strategies for Troops Returning From Iraq and Afghanistan and Their Families*. Berkeley, CA: Ulysses Press, 2006: 239 pp.
- Vogt DS, et al. Deployment stressors, gender, and mental health outcomes among Gulf War I veterans. *J Traumatic Stress.* 2005;18:115-127.



THE KNEE- Narrowing differential to facilitate appropriate management

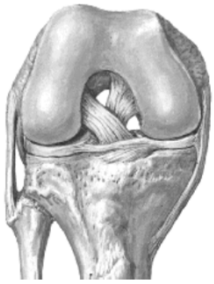
John O' Kane MD
Associate Professor U.W. Family Medicine and Orthopedics

Overview

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

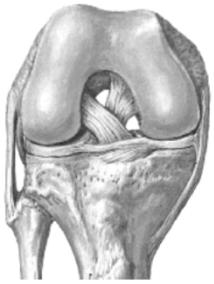
Menisci

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



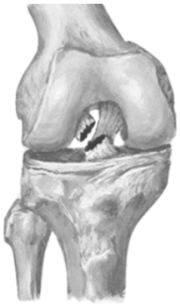
Collateral Ligaments

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



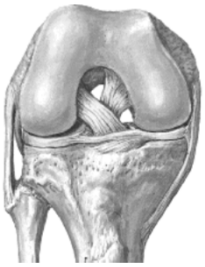
Anterior Cruciate Ligament

- 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

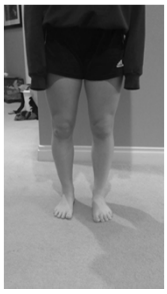
- VMO
  - Absorbs eccentric load and controls patellar tracking
- Gluteus medius and hip ext. rotators
  - Controls knee rotation and valgus alignment
- Hamstrings
  - Prevent anterior tibial translation which protects ACL

Physical exam

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

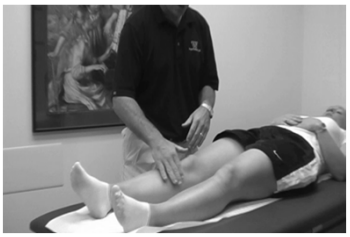
Physical Exam

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



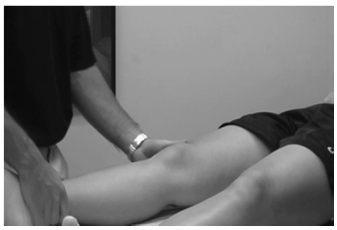
Physical Exam

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



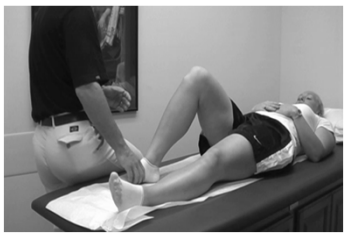
Physical Exam- Stability

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



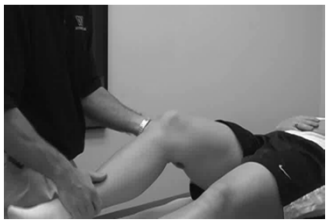
Physical Exam- Stability

- 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



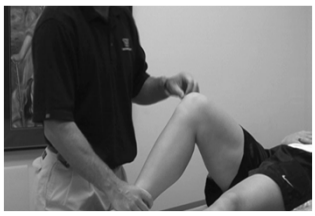
Physical Exam- Stability

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

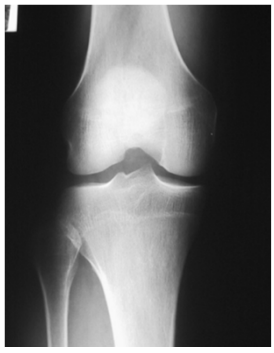


Physical Exam- McMurray's

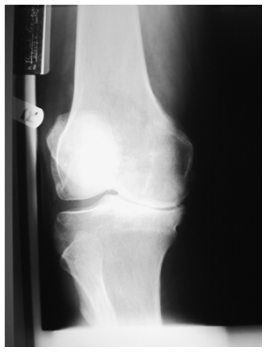
- thumb- MJL, long finger- LJL
- flex knee, internal and external rotation
- extend knee with varus then valgus with leg in internal and external rotation
- Click, pop, or pain is + test



Imaging- Plain XR WB



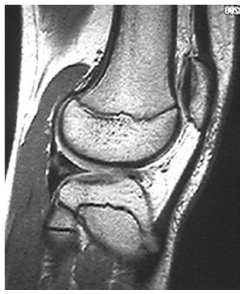
Notch view-normal



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



Sagital- 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

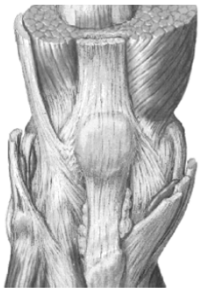
- Key Features
  - insidious onset, no trauma
  - history of "training error"
  - no effusion or significant mechanical symptoms
  - worse with activity, improves with rest
- Imaging
  - Rarely at initial visit
  - Caveat: joint pain >age 50 should be x-rayed
- Consultation
  - Physical Therapy

Overuse / Biomechanical

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

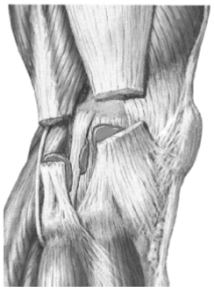
Differential Diagnosis by Location

- Anterior
  - Patellofemoral/ chondromalacia
  - Patella tendonitis



Differential Diagnosis by Location

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



Differential Diagnosis by Location

- 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

Thank you

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
Women's Health Care Center, UWMC
Associate Professor, Dept of Medicine, UW
esutton@uw.edu

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

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

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

Common symptoms of menopause

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

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

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

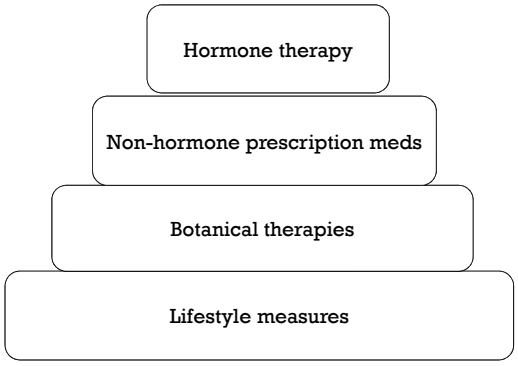
- Which of the following additional history is important to guide discussion of therapeutic options with her?

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

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

"Step therapy" for VMS



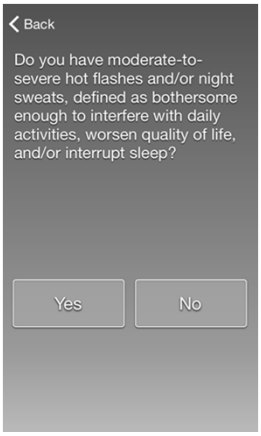
There's an app for that!

- MenoPro: Appfor iPhone/iPad released in 2014
- by North American Menopause Society (NAMS)

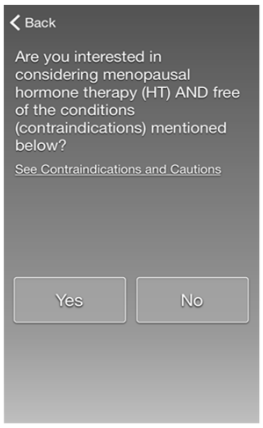
- Goal: help individualize treatment based on pt's preferences & risk factors.

- Pros: Developed by a medical society
- Free, with no ads or industry support
- Assesses menopause status, symptom severity, & risks
- Provides educational info: lifestyle, diet, & behav. modifications
- Includes tables on risks/benefits of medications
  Includes risk calculators

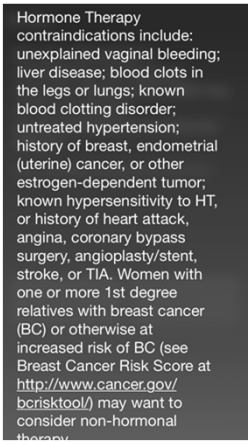
- Limitations: Currently only available for iPhone/iPad
- Text is college-level to graduate school-level



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?



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…

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-HT_{1A}, 5-HT_{1D} and 5-HT_7) (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

- Drew et al, A systematic review of non-hormonal treatments of vasomotor symptoms in climacteric and cancer patients. Springerplus 2015 Feb 10;4:65.

Non-hormonal Rx*

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

*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)

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

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
- Cochrane Review 3/2015 on HT for CVD prevention after menopause concludes: Don't.
- 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

$150/mo

Common symptoms of menopause

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

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

Osphena®: ospemifene

- Dose: 60 mg by mouth once daily
- Cost: $200/month
- Ospemifene, 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
- Rahn et al, Vaginal estrogen for genitourinary syndrome of menopause: a systematic review. Obstet Gynecol 12/2014

Topical estrogen for GU atrophy

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

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

13-18 Years

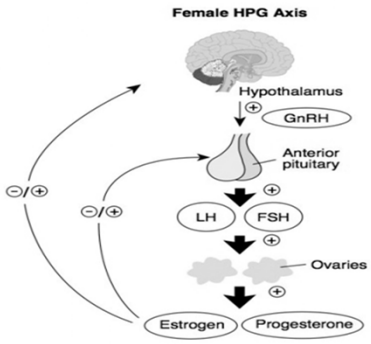
- Anovulation
- Coagulopathy
- Pregnancy
- Pelvic Infection

19-39 Years

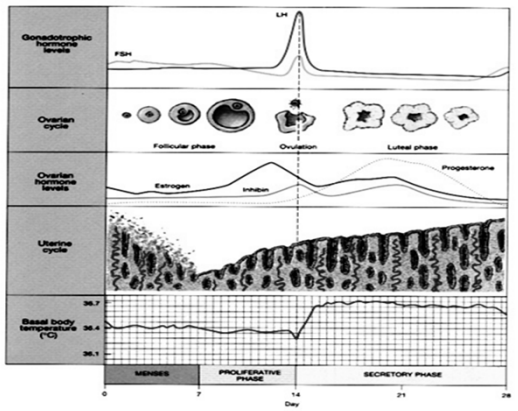
- Pregnancy
- Leiomyomas
- Polyps
- Anovulatory cycles
- Hormonal contraception
- Endometrial hyperplasia

40 Years to Womenopause

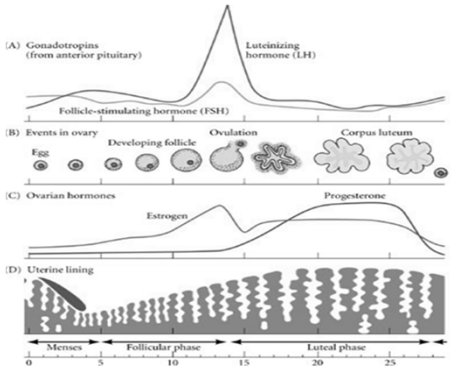
- Anovulation
- Endometrial hyperplasia
- Polyp
- Leiomyoma



A Hiller-Sturmhofer et al. 1998

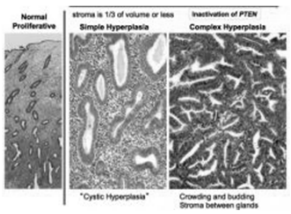


Menstrual Symphony



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 Ag, Ristocetin cofactor
- US – TVUS v. Saline infusion
- Endometrial biopsy
- Hysteroscopy
- D&C

Case 1: Early Reproductive Age

CC: 13 yo with heavy menses every 6-12 wks

HPI: Soaking through pads and underwear at night

No ER visits for this

Menarche: 12

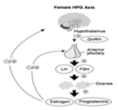
Not sexually active

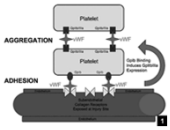
No medications

No change in weight

Age-Based Differential Dx

- Anovulation (AUB-O) due to hypothalamic immaturity
  - 70% are regular by 3rd year of menses
  - Anorexia, bulemia
- 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

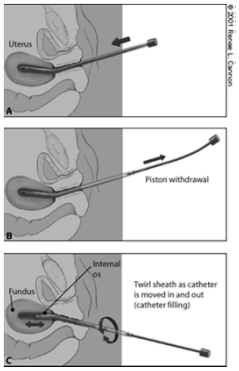
To EMB or Not to EMB….

To rule out hyperplasia or cancer

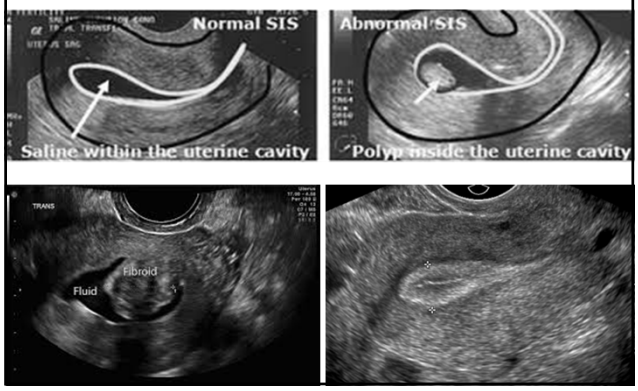
Older than age 45

Or any patient with:

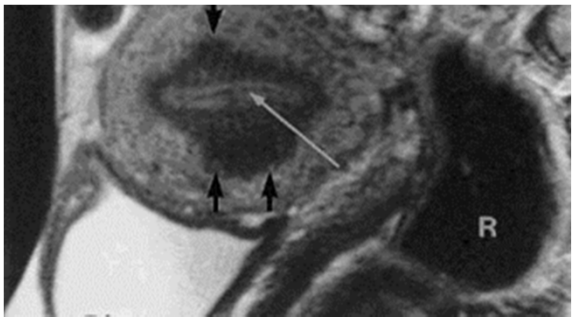
Unopposed estrogen
Failed medical management
Persistent AUB



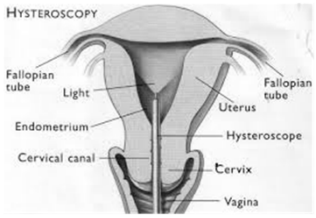
Imaging

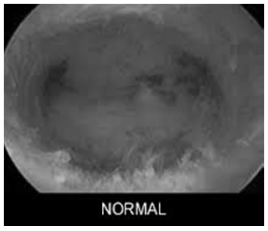


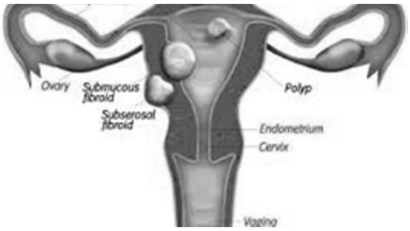
Imaging-MRI



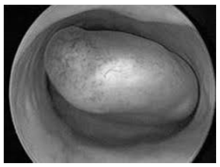
Hysteroscopy

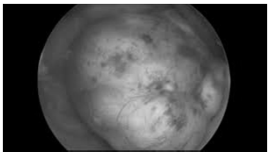






Hysteroscopy





Treatment

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

AUB-O (Ovulatory Dysfunction)

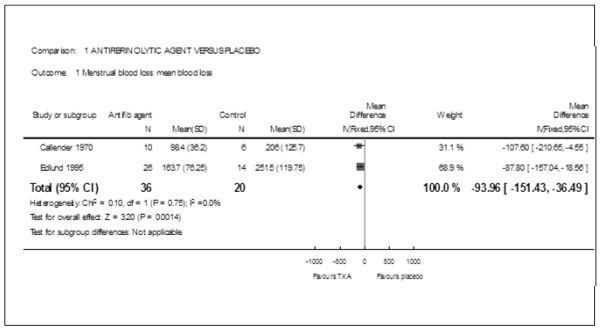
- Most common cause
- Non-Acute
- Medical Treatment
  - NSAIDS
  - OCPs (cyclic or continuous)
  - Oral Progestin (cyclic or continuous)
  - Progesterone IUD
  - Anti-fibrinolytics - Tranexamic Acid
  - GnRH Agonists/Antagonists

NSAIDS

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

Duckett and Farquar Cochrane 2013

TRANEXAMIC ACID



Lethaby, Farquar and Cooke Cochrane Review 2010

OCP vs. PLACEBO

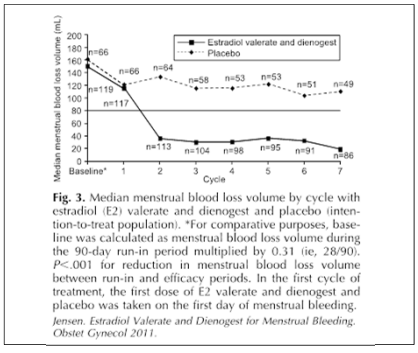


Fig. 3. Median menstrual blood loss volume by cycle with estradiol (E2) valerate and dienogest and placebo (intention-to-treat population). *For comparative purposes, baseline was calculated as menstrual blood loss volume during the 90-day run-in period multiplied by 0.31 (ie, 28/90). $P<.001$ for reduction in menstrual blood loss volume between run-in and efficacy periods. In the first cycle of treatment, the first dose of E2 valerate and dienogest and placebo was taken on the first day of menstrual bleeding.

Jensen. Estradiol Valerate and Dienogest 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%

Shaaban et al 2011. Contraception
Irvine et al 1998. BJOG

LEVONORGESTREL IUD

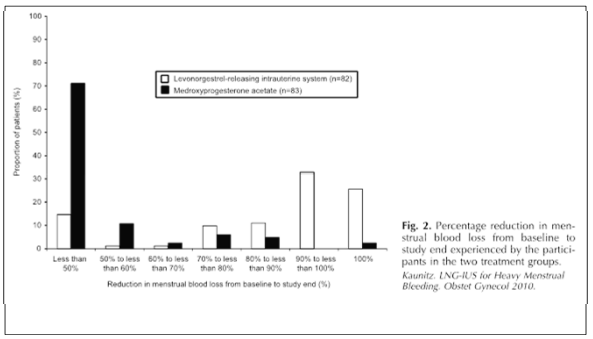


Fig. 2. Percentage reduction in menstrual blood loss from baseline to study end experienced by the participants in the two treatment groups.
Kaunitz. LNG-IUS for Heavy Menstrual Bleeding. Obstet Gynecol 2010.

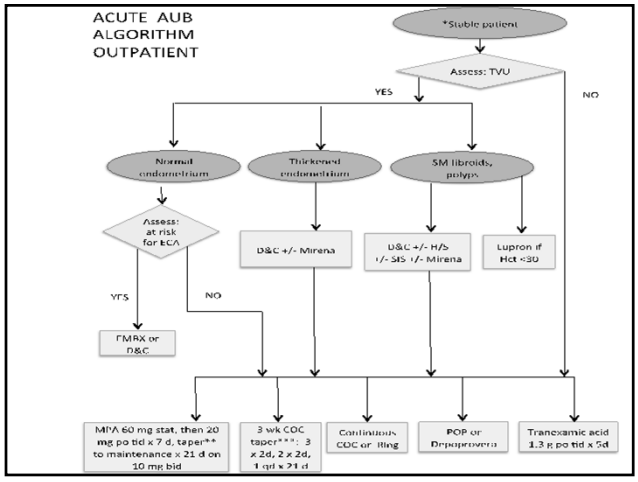
Table 2. Medical Management of Abnormal Uterine Bleeding

Intervention A	Intervention B	Preferred Intervention (Level of Evidence)	Clinical Practice Guideline Statements for the Reduction in Mean Blood Loss
LNG-IUS	OCPs	LNG-IUS (1B)	We recommend the use of LNG-IUS over OCPs, luteal-phase progestins, and NSAIDs
	Luteal oral progestin	LNG-IUS (1B)	
	Extended oral progestin	Either (2C)	
	Antifibrinolytics	No direct comparison*	
	NSAID	LNG-IUS (2C)	
OCPs	LNG-IUS	LNG-IUS (1B)	We recommend the use of LNG-IUS over OCPs; we suggest the use of OCPs over luteal-phase progestins
	Luteal oral progestin	No direct comparison*	
	Extended oral progestin	No direct comparison*	
	Antifibrinolytics	No direct comparison*	
	NSAID	Insufficient data† (2D)	
Luteal-phase oral progestin	LNG-IUS	LNG-IUS (1B)	We recommend the use of LNG-IUS over luteal-phase progestins; we suggest the use of OCPs and antifibrinolytics over luteal-phase progestins
	OCPs	No direct comparison*	
	Extended oral progestin	No direct comparison*	
	Antifibrinolytics	Antifibrinolytic (2D)	
	NSAID	Insufficient data (2C)	
Extended cycle oral progestin	LNG-IUS	Either (2C)	There are insufficient data on which to make suggestions
	OCPs	No direct comparison*	
	Luteal oral progestin	No direct comparison*	
	Antifibrinolytics	No direct comparison*	
	NSAID	No direct comparison*	
Antifibrinolytics	LNG-IUS	No direct comparison*	We suggest the use of antifibrinolytics over luteal-phase progestins and NSAIDs
	OCPs	No direct comparison*	
	Extended oral progestin	Antifibrinolytic (2D)	
	Luteal oral progestin	No direct comparison*	
	NSAID	Antifibrinolytic (1B)	

Matteson et al. Obstet Gynecol 2013 ;121:632-43

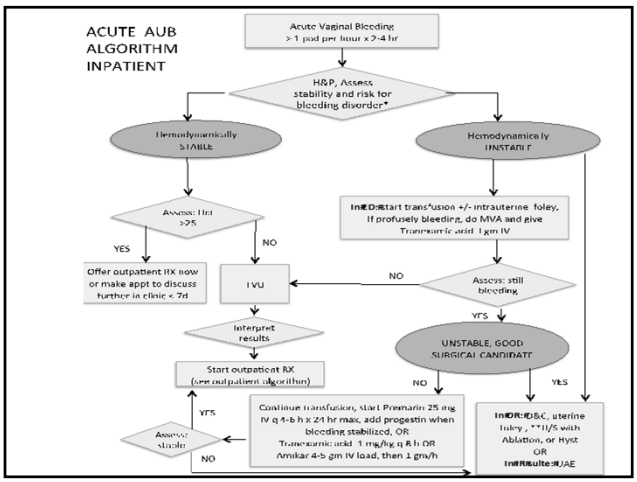
Treatment - Surgical

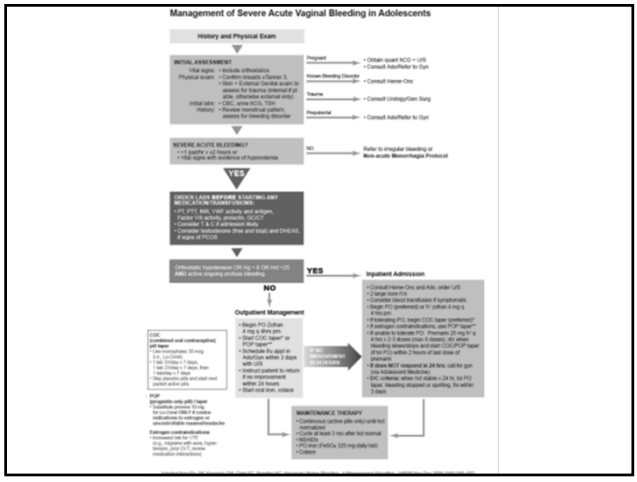
- Dilation and Curettage
- Endometrial ablation
- Hysteroscopic resection of lesions
- Hysterectomy



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

- Matteson K. ACOG Committtee Opinion 557, April 2013. Management of Acute Abnormal Uterine Bleeding in nonpregnant Reproductive-Aged Women.
- Munro MG. Southern California Permanente Medical Group's Abnormal Uterine Bleeding Working Group. Acute Uterine Bleeding unrelated to pregnancy: a Southern California Permanente Medical Group Practice guideline. Perm J. 2013 Summer;17(3):43-56.
- Munro MG. FIGO Classification system (PALM-COEIN for causes of abnormal uterine bleeding in nongravid women of reproductive age. IJOG 2011 April;113(1):3-13