Women’s Health: Year in Review

Judith Walsh, MD, MPH
Professor of Medicine
Division of General Internal Medicine
UCSF Women’s Health Center of Excellence

Plan for today...

• Review some of the most significant published advances in the Women’s Health medical literature over the past year
  • Top articles
  • Key articles
  • Guidelines

• Assess the strength and scope of the evidence presented in the selected literature

• Apply this new information to our clinical practice
  • Take-home points

How did we choose our articles?

• Systematic review of 15 top journals in General Internal Medicine and Women’s Health from March 2015–February 2016

• Articles chosen had to fulfill criteria:
  • How new/innovative is this information?
  • Strength of the evidence?
  • How will it change my practice?
Topics for Today

• Breast Cancer Prevention
• UTIs and STIs
• Bone Health
• Menopause Management
• Ovarian Cancer Screening and Prevention

Breast Cancer Prevention

Case

A 39 year old woman is very worried about her risk of breast cancer. Her mother and sister both had breast cancer; her sister tested negative for a known gene mutation. Using an online breast cancer risk calculator, you estimate her 5 year risk of breast cancer to be 3%.

Is she a candidate for chemoprophylaxis to decrease her breast cancer risk?

A. Yes
B. No
C. Maybe

Background

• Four RCTs have shown that tamoxifen can reduce the risk of breast cancer in women at increased risk in the first 10 years of follow up
• Infrequently prescribed
• Limitations and surprising results of the first International Breast cancer Intervention Study (IBIS) report
  • increased deaths, though not statistically significant
The News

- Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-I breast cancer prevention trial
- Objectives
  - Long-term follow-up after tamoxifen treatment to determine impact on occurrence and mortality of invasive breast cancer and DCIS

Methods

- N=7154 women aged 35-70
- Blindly randomized to oral tamoxifen 20 mg daily vs placebo for 5 years
- Inclusion criteria
  - Aged 45-70: ≥2x risk
  - Aged 35-44: >2x risk
- Exclusions: h/o DVT, PE, desired pregnancy, h/o cancer

Results

- Median follow up 16 years. 74% still masked to assignment
- Placebo group: 9.8% of women developed breast cancer
- Tamoxifen group: 7% of women
- Hazard ratio 0.71 (p<0.0001)
- HR is the same for the first ten years and 10+ years
- Women receiving HT had less benefit
  - Hot flashes during active treatment
  - DVTs OR 1.73 (increased during first 10 years only)
  - Endometrial cancer during active treatment only (2.5 excess cases per thousand women)

Conclusions

- Tamoxifen x 5 years offers a very long period of protection, substantially improving the benefit-to-harm ratio
- NNT 22 to prevent one case of breast cancer in 20 years
- NNT 29 to prevent one case of estrogen receptor positive invasive breast cancer in 20 years
- No difference in breast cancer mortality (underpowered)
Take-Home

- Women with extremely high risk (BRCA1 or BRCA2 gene mutations or other familial syndrome) should be counseled on prophylactic mastectomy
- Consider tamoxifen for women at otherwise increased risk (using BCSC tool, or http://www.cancer.gov/bcrisktool/Default.aspx)
- USPSTF 2013 (B recommendation): For women at increased risk of breast cancer and low risk for adverse medication effects, clinicians should offer tamoxifen or raloxifene

Case

A 39 year old woman is very worried about her risk of breast cancer. Her mother and sister both had breast cancer; her sister tested negative for a known gene mutation. Using an online breast cancer risk calculator, you estimate her 5 year risk of breast cancer to be 3%.

Is she a candidate for chemoprophylaxis to decrease her breast cancer risk?
- a) Yes
- b) No
- c) Maybe – refer to genetic counselor/high risk breast clinic

UTIs and STIs

Case

Nellie Natural is here for her annual visit. She mentions mild UTI symptoms for 4 days. UA is + for LE and nitrites. She’s not a fan of medications, tends to prefer “natural supplements”, and asks you if antibiotics are truly necessary. You tell her:

- A. Antibiotics may lower her risk of pyelonephritis
- B. She can try ibuprofen 400 tid instead of an antibiotic
- C. More than 2/3 of typical UTIs resolve on their own
- D. All of the above
The News

- Ibuprofen versus fosfomycin for uncomplicated urinary tract infection in women: randomised controlled trial.

- Objective:
  Can uncomplicated UTI be treated with ibuprofen to reduce antibiotic prescriptions without a significant increase in symptoms, recurrences, or complications?

Methods

- Study Design:
  - Double blind randomized multicenter trial of 42 GPs in Germany

- Intervention:
  - 779 women, up to age 65, with suspected UTI randomized
  - Fosfomycin 3 g sachet x 1 day or
  - Ibuprofen 400 tid x 3 days

- Women scored their daily symptoms and activity impairment

- Safety data collected q 6mo, between 2012-2014

- Inclusion criteria:
  - Dysuria, frequency, urgency, +/- lower abdominal pain

- Exclusion criteria:
  - Fever, “loin” tenderness
  - Pregnancy, renal disease
  - UTI within 2 wks
  - Urinary catheterization
  - Contraindication to NSAIDs

Results:

<table>
<thead>
<tr>
<th>Select outcome</th>
<th>Ibuprofen n=241</th>
<th>Fosfomycin n=243</th>
<th>RR 66.5% (58.8-74.4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Courses of antibiotic within 28d</td>
<td>81</td>
<td>277</td>
<td></td>
</tr>
<tr>
<td>Mean duration of symptoms</td>
<td>5.6 days</td>
<td>4.6 days</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>% Patients symptoms–free at day 7</td>
<td>70%</td>
<td>82%</td>
<td>P=0.004</td>
</tr>
<tr>
<td>% Patients with recurrence of UTI (d 15-28)</td>
<td>6%</td>
<td>11%</td>
<td>P=0.049</td>
</tr>
<tr>
<td>Number of patients with pyelonephritis</td>
<td>5</td>
<td>1</td>
<td>P=0.12</td>
</tr>
<tr>
<td>Number of patients with GI symptoms</td>
<td>6</td>
<td>15</td>
<td>NS</td>
</tr>
</tbody>
</table>

Conclusions

- Women with mild to moderate symptoms may benefit
  - Nonparticipants had higher symptom scores

Reminder:

Treatment of asymptomatic bacteruria not recommended. 2015 Cochrane review showed no benefit of antibiotics to prevent:
  - Symptomatic UTI
  - Complications
  - Death

Take-Home

- Nellie can try ibuprofen for her UTI. She should be counseled to call if her symptoms persist, and to watch for possible pyelonephritis.
  - Two-thirds of UTIs resolved on their own
- Women who take ibuprofen are more likely to need additional antibiotic therapy, but still less likely to receive antibiotics overall.

The News

- **NEW** CDC STD treatment guidelines in 2015
  - Gonorrhea now requires DUAL therapy on SAME day:
    - Ceftriaxone 250mg IM single dose + Azithro 1 gm orally
    - Azithromycin 2gm is NO longer an acceptable therapy

Bone Health

Case

Frances Fragile is a 67 year old woman who has just come in to establish care with you. She has never had a DXA scan and you order one. You are on your way out the door when she asks whether or not you are going to check her Vitamin D level. Her sister told her that she is supposed to have a level of 30 ng/ml. What do you say?

A. Of course. We should check Vitamin D levels in everyone
B. No. Just be sure you are taking a Vitamin D supplement of 800 IU a day.
C. We will check your Vitamin D level if your DXA scan shows osteoporosis.
D. I don’t know. What do you want to do?
Background

- Low Vitamin D levels contribute to osteoporosis
- The optimal Vitamin D level for skeletal health is debated
  - >30 ng/ml recommended by some
  - >20 ng/dl recommended by IOM
- Using a definition of Vitamin D deficiency of <30ng/ml, 75% of postmenopausal women would be deficient
- Determining the optimal level of 25 (OH) D for bone health and optimal calcium homeostasis is important

The News

- “Treatment of Vitamin D Insufficiency in Postmenopausal Women: A Randomized Controlled Trial”
  - Hansen et al. JAMA Intern Med. 2015

Objectives

- To evaluate the impact of low dose and high dose cholecalciferol compared with placebo in postmenopausal women with Vitamin D deficiency on the following outcomes:
  - changes in fractional calcium absorption,
  - Bone mineral density and muscle mass
  - Timed Up and Go tests and five sit to stand tests
  - Functional status and physical activity

Methods

- Single center randomized double blind controlled trial
- Participants:
  - 230 postmenopausal women without osteoporosis
  - 75 years or younger
  - Baseline Vitamin D levels 14-27 ng/dl
- Intervention
  - 800 IU Vitamin D3 daily
  - 50,000 IU Vitamin D3 twice a month
  - Achieved and maintained Vitamin D levels ≥30 ng/dl
  - Placebo
- Outcomes measured at 1 year

Results

- Calcium absorption (change from baseline):
  - Increased by 1% in the high dose arm (10 mg/day)
  - Decreased by 2% in low dose arm (P=0.005 low vs high dose)
  - Decreased by 1.3% in placebo arm (P<0.03 placebo vs high dose)
- BMD or muscle mass scores:
  - No between arm differences in any comparisons
- Timed Up and Go or five sit to stand tests
  - No between arm differences in any comparisons
- ALSO NO differences in:
  - number of falls
  - number of people who fell
  - functional status
  - physical activity
Conclusions

- Although high dose cholecalciferol therapy increased calcium absorption, there was no impact on bone density or other clinically important outcomes.
- Low and high dose cholecalciferol were equivalent to placebo with respect to effects on bone and muscle outcomes.

Take-Home

- No evidence supports recommendations for maintaining serum 25 (OH) levels >30 ng/ml

Back to Frances

- You tell Frances that there is no evidence that a Vitamin D level of >30 ng/ml is necessary for bone health, but she wants to know if there are other benefits to Vitamin D supplementation that she should know about.

Vitamin D and Functional Decline?

- RCT conducted in Switzerland
  - 200 men and women ≥70 with prior fall
  - Three groups received monthly treatment
    - 24,000 IU Vit D3
    - 60,000 IU Vit D3
    - 24,000 Vit D3 plus 300µg calcifediol
- Outcomes
  - Higher doses were more likely to result in 25-OH D ≥30 ng/ml
  - No impact on lower extremity function
  - More falls in the higher dose groups.
    - Bischoff Ferrari et al JAMA Int Med 2016
Exercise, Vitamin D and Fall Prevention

- Two year RCT of exercise and Vitamin D supplementation in Finland
- Four groups:
  - Vitamin D 800 IU without exercise
  - Vitamin D 800 IU with exercise
  - Placebo and exercise
  - Placebo and no exercise
- Outcomes: monthly reported falls, injurious falls, number of fallers and injured fallers
- Neither Vitamin D nor exercise reduced rate of falls
- Rate of injurious falls significantly decreased with strength/balance/exercise training
  - Uusi-Rasi K et al JAMA Int Med 2015

Case: Ms. Fragile, continued

- On further questioning, Ms. Fragile tells you that she has been taking calcium supplements for years because she is very concerned about osteoporosis. Recently, she has heard that calcium supplements might actually be bad for her and that she might be better off getting all her calcium from her diet.
- She wants to know what you recommend.

Background

- Calcium supplementation has been widely recommended for bone health
- Clinical trials of calcium supplementation of 1000 mg/day have suggested an increase in cardiovascular events, kidney stones and GI symptoms
- Current recommendations often focus on telling patients to increase calcium intake through diet rather than supplements
  - Assumption that this increases calcium intake to recommended goals without the adverse effects of supplements

The News

- “Calcium intake and risk of fracture: systematic review”
  - Boland et al. BMJ, 2015
- Objectives:
  - To evaluate the evidence underlying recommendations to increase calcium intake through diet or calcium supplements in order to prevent fracture
Methods

- Systematic review
- RCTs in adults >50 at baseline with endpoint of fracture
- Cohort studies where most follow-up occurred in participants >50 years
- Studies where calcium was given with another treatment assuming treatment was given in both arms
- Included studies with calcium and Vitamin D co-administered
- Dietary calcium included milk, dairy, dietary intake from food and hydroxyapatite
- Meta-analyses with random effects and assessed for heterogeneity

Results: Dietary Calcium

- Two RCTS and 44 cohort studies assessed relationship between dietary calcium (n=37), milk (n=14), or dairy intake (n=8) and fracture outcomes
- Dietary calcium: most studies showed no association with fracture
  - 14/22 for total
  - 17/21 for hip
  - 7/8 for vertebral
  - 5/7 for forearm
- Milk and dairy intake: most studies showed no association with fracture
  - 25/28 milk
  - 11/13 dairy
- Too few trials to calculate summary estimate

Results: Calcium Supplements

- 26 RCTS reported fracture outcomes
  - 14 calcium only
  - 8 Ca/D
  - 4 were multi-arm or factorial of both
  - 20 trials used a dose of ≥1,000 mg of calcium
- Fracture reduction
  - Reduced risk of total fracture (RR 0.89: 95% C.I. 0.81-0.96)
  - Reduced risk of vertebral fracture (0.87: 95% C.I. 0.74-1.00)
  - No reduction in hip or forearm fracture
- Funnel plot inspection suggested bias toward calcium supplements
  - Studies with lowest risk of bias showed no effect on fracture

Conclusion

- Dietary calcium is not associated with fracture risk
- There is no clinical trial evidence that dietary calcium reduces fracture risk
- Some evidence that calcium supplementation reduces fracture risk but evidence is inconsistent
Calcium intake and bone mineral density

- Meta-analysis of the impact of dietary or supplemental calcium on BMD
  - Tai et al BMJ 2015
  - 59 eligible RCTs
    - 15 dietary calcium
    - 51 supplemental calcium
  - Increasing calcium intake from dietary sources increased BMD
    - 0.6-1.0% at total hip and total body at one year
    - 0.7-1.8% at these sites at two years
  - Calcium supplements increased BMD similarly
  - BMD increases similar for dietary and supplemental calcium and for Ca/D
  - Dietary and supplemental calcium lead to small nonprogressive increases in BMD—clinical significance is unclear

Impact for Practice

- Dietary and supplemental calcium lead to small increases in BMD
- There is no clinical trial evidence that dietary calcium reduces fracture risk
  - Dietary studies have challenges
- The evidence for calcium supplements and fracture reduction is mixed
- There is no evidence that dietary calcium is more effective than supplemental calcium

Case

- Bonnie Bony is a 76 year old woman who has been on alendronate for 5 years after having a hip T-score of -2.8. She also has diabetes and hypertension. Her best friend, Veronica Vertebrae, just stopped her bisphosphonate because she developed osteonecrosis of the jaw (ONJ). Bonnie wants to know if she should continue taking the alendronate or whether she should stop. What do you tell her?

The News

- Objective:
  - To provide guidance on bisphosphonate therapy duration with a risk-benefit perspective
Background

- Age is the greatest risk factor for fracture
- Whether or not continued bisphosphonate therapy continues to confer benefit is debated
- Rare but real side effects
  - Jaw osteonecrosis
  - Atypical femoral fractures
- How long should women remain on therapy?
  - Drug holidays?
- FDA “Limitation of Use Statement”
  - Optimal duration of use has not been determined
  - “All patients on bisphosphonates should have the need for continued therapy reevaluated on a periodic basis”

Methods

- Systematic literature reviews
- Two RCTS (FLEX and HORIZON) provide evidence on long term use
- Evaluation of benefits and risks of bisphosphonates and alternatives

Recommendations

- After 5 years of oral bisphosphonates or 3 years of IV bisphosphonates, reassessment of risk should be considered
  - In women at high fracture risk, consider continuation of oral BP for 10 years or IV BP for 6 years
    - High risk based on age (>70 or 75), medication use, new dx of disorder associated with secondary osteoporosis
    - Clinician deemed high risk based on femoral neck T score, age or other risk factors
  - For women not at high fracture risk after 3-5 years of treatment, consider a drug holiday of 2-3 years
  - For high risk women, risks of atypical femoral fracture and ONJ are outweighed by reduction in vertebral fracture

What is “high risk?”

- Older women (>70 or 75)
- Low hip T score or high fracture risk score (FRAX criteria)
- Previous osteoporotic major fracture
- Fracture on therapy
- Limitations
  - Limited evidence
  - White postmenopausal women
  - Vertebral fracture reduction only
Impact for practice

• Patients at “low risk” may safely have bisphosphonates discontinued
  • Younger, no fracture history, medication was started for osteopenia, BMD approaching normal?
• Patients at “increased risk” may benefit from continued therapy
  • Older, history of fracture, BMD remaining in osteoporotic range?
• Decisions about when to restart?
  • Role of BMD
  • Currently, no evidence to support use of bone turnover markers

Let’s ask the dog…..

Menopause Management
Case

• Minnie Pause is a 65 year old woman who continues to have intolerable hot flashes. She wakes up several times a night and is at her wits end. She has tried complementary therapies and most recently took paroxetine for these symptoms but they are unrelenting. She wants to know whether or not estrogen is an option for her.

The News

• “North American Menopause Society Statement on Continuing Use of Systemic Hormone Therapy After Age 65”
  • Menopause, 2015
  • Statement:
    • Provided that the woman has been advised of the increase in risks associated with continuing HT beyond age 60 and has clinical supervision, extending HT use with the lowest effective dose is acceptable under some circumstances, such as for the woman who has persistent bothersome menopausal symptoms and for whom her clinician has determined that the benefits of menopause symptom relief outweigh the risks.
    • Use of HT should be individualized and not discontinued solely based on a woman’s age.
    • Decision to continue or discontinue should be made jointly

Case

• Hortense Flash is a 56 year old woman who has had hot flashes for the past 2 years. Although she had hoped they might improve, they have not changed. She adamantly does not want to take estrogen and wonders what else will really work for her.

The News

  • Menopause, 2015
  • Objective
    • To update and expand the NAMS evidence-based position on nonhormonal management of menopause-associated vasomotor symptoms
Methods

- Systematic review of nonhormonal menopause treatments
- Costs, time, effort and adverse effects weighed against potential effectiveness
- Divided into categories
  - Recommended
  - Recommend with caution
  - Do not recommend at this time

Results

- Recommended
  - Cognitive behavioral therapy and hypnosis
  - Paroxetine is the only FDA-approved non-hormonal treatment
  - Other SSRIs, SNRIs, gabapentin and clonidine have shown efficacy
- Recommend with caution
  - Weight loss
  - Mindfulness-based stress reduction
  - Sequal derivatives of soy isoflavones
  - Stellate ganglion block
- Do not recommend at this time
  - Cooling techniques, avoidance of triggers, exercise, yoga, paced respiration, relaxation, OTC supplements and herbal remedies, acupuncture, chiropractic, calibration of neural oscillations

Impact for practice

- When recommending nonhormonal treatments for menopause, clinicians should be aware of the limited evidence supporting them
- Although many proposed menopause treatments may not have been proven to be beneficial for VMS treatment, some may be relatively benign (eg cooling techniques) or have other benefits (e.g. yoga and exercise)

Ovarian Cancer Screening & Prevention
Case

Ana Lee comes to clinic requesting screening for ovarian cancer. A friend recently forwarded her an email which reads: "Please tell all your female friends and relatives to insist on a CA-125 blood test every year as part of their annual exam. This is an inexpensive and simple blood test. Don't take 'No' for an answer. If I had known then what I know now, we would have caught my cancer much earlier before it was Stage 3!"

Clinical Question

Do you order:
A. A serum CA-125
B. A transvaginal ultrasound
C. Testing for BrCA1
D. More teal ribbons
E. None of the above

Background

- Ovarian cancer is most deadly of female reproductive cancers
- Each year, 22,000 US women diagnosed with ovarian cancer
- In 2011, the Prostate Lung Colorectal Ovarian (PLCO) Cancer Screening trial, reported no benefit of screening over 78,000 women followed for over a decade...
  - Was the study underpowered?
  - Would a "risk of ovarian cancer algorithm" that considered longitudinal changes in CA-125 be more useful??

The News

- “Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKTOCS): a randomized controlled trial”
- Objectives
  - To assess the impact of annual screening for ovarian cancer using transvaginal ultrasound with and without serum Ca-125 levels interpreted using a "risk of ovarian cancer algorithm" on:
    - Ovarian cancer mortality
    - Death due to ovarian or primary peritoneal cancer
    - Complications due to screening and false positives
Methods

- 202,638 postmenopausal women aged 50-74
- 27 primary care trusts in England, Wales, Ireland
- No history of oophorectomy, ovarian cancer or other active cancer
- Randomized trial
  - 50% no screening
  - 25% annual transvaginal ultrasound
  - 25% annual transvaginal ultrasound + CA-125
    - Interpreted using the patented “Risk of Ovarian Cancer Algorithm”
- Outcomes committee was masked,
- Participants and their clinicians were not blinded
- Followed for 10-12 years (median 11.1 years)

Results

- Ovarian cancer mortality? **No difference**
- Ovarian or primary peritoneal cancer mortality? **No**

<table>
<thead>
<tr>
<th>Per 100,000 woman years</th>
<th>Ovarian CA Incidence</th>
<th>False positive surgeries</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Screening</td>
<td>57</td>
<td>0</td>
</tr>
<tr>
<td>Annual US</td>
<td>57</td>
<td>500</td>
</tr>
<tr>
<td>Annual US +CA-125</td>
<td>62</td>
<td>140</td>
</tr>
</tbody>
</table>

**IF excluded prevalent cases AND deaths in first 7 years...**

*Maybe?? But NNT>2000 for 10 years*

Conclusions

- **Still** no good way to screen for ovarian cancer
- Focus on Prevention
  - Anything that suppresses ovulation
    - Hormonal contraception
    - Pregnancy & Lactation
Take-Home

- Consider tamoxifen or raloxifene in high risk women
- Two thirds of UTIS will resolve without treatment
- No evidence to support maintaining a Vitamin D level ≥ 30 mcg/dl
- Consider hormonal treatment for menopausal symptoms for appropriate women regardless of age
- When prescribing nonhormonal treatments for menopause, clinicians should be aware of the evidence supporting them
- No evidence for using transvaginal US or CA-125 to screen for ovarian cancer

Questions?