Update in Women’s Health: Year in Review

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Background

• Annual Update in Women’s Health for Society of General Internal Medicine
• Collaborators
  • Megan McNamara, MD, MAS, Case Western
  • Kay Johnson, MD, University of Washington
  • Pelin Batur, MD, Cleveland Clinic
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 16 top journals in General Internal Medicine and Women’s Health from March 2014 – February 2015

• Articles chosen had to fulfill two criteria:
  • How new/innovative is this information?
  • How will it change my practice?
Contraception

Case

• Ms Whoopsy Daisy is a 25-year-old female who seeks advice regarding effective emergency contraception (EC). Her PMH includes obesity (BMI 35). The condom broke 3 nights ago during intercourse with her boyfriend. She would like something highly effective, as she does not want to become pregnant. You recommend ulipristal acetate, but she has safety concerns because it is a newer product. At this time you:

A. Suggest a levonorgestrel releasing IUD given it’s the most effective form of EC

B. Reassure her of the safety of ulipristal in postmarketing reports

C. Proceed with levonorgestrel (Plan B)

D. Prescribe ulipristal, noting its safety to her, but warn her of a possible abortifacient potential
The News

- *Ulipristal acetate for emergency contraception: postmarketing experience after use by more than 1 million women*
  - Levy et al. Contraception 2014

- Objective:
  - Describe the safety of ulipristal acetate in emergency contraception

Background

- In the US 4 EC methods are available. All used within 5 days of intercourse. In order of most to least effective:
  - copper IUD (99.9% effective)
  - ulipristal acetate 30 mg (an anti-progestin pill)
  - levonorgestrel 1.5 mg (a progestin-only pill)
  - the Yuzpe method (oral contraceptives taken in various combinations)

- The pills work by preventing ovulation¹-³
  - They are not effective after ovulation
  - Can’t disrupt an established pregnancy, not abortifacient
  - No medical contraindications

- Ulipristal acetate (ella™) is a newer product
  - European approval 5/2009
  - US approval 8/2010

3. ACOG Committee Opinion No 542
Methods

- Manufacturer's postmarketing surveillance data gathered via:
  - reports received from health care professionals
  - review of the medical literature
  - reports received from regulatory authorities

- Review of all pregnancies that have occurred during the developmental program of UPA
  - for EC (30 mg single dose) or
  - treatment of uterine fibroids (5 mg daily doses)

Results:

- >1,400,000 women exposed to UPA for EC worldwide

- Few serious events reported (other than pregnancy)
  - 282 pregnancies
  - Pregnancy was the commonest “SAE”
Results: Common Adverse Drug Reactions (ADRs)

Most common suspected ADRs reported after 1.4 million exposed to UPA 30 mg from launch in October 2009 to May 2013*

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Number (of 1049 total ADRs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>282 (26.9%)</td>
</tr>
<tr>
<td>Gastrointestinal system</td>
<td>139 (13.3%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>62</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>38</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12</td>
</tr>
<tr>
<td>Abdominal pain, upper</td>
<td>16</td>
</tr>
<tr>
<td>Abdominal pain, lower</td>
<td>11</td>
</tr>
<tr>
<td>Nervous system</td>
<td>67 (6.4%)</td>
</tr>
<tr>
<td>Headache</td>
<td>47</td>
</tr>
<tr>
<td>Dizziness</td>
<td>20</td>
</tr>
<tr>
<td>Reproductive system</td>
<td>84 (8.0%)</td>
</tr>
<tr>
<td>Metrorrhagia</td>
<td>21</td>
</tr>
<tr>
<td>Genital hemorrhage</td>
<td>26</td>
</tr>
<tr>
<td>Menses delay</td>
<td>19</td>
</tr>
<tr>
<td>Breast symptom (disorder, tenderness, tension, pain)</td>
<td>18</td>
</tr>
</tbody>
</table>

*D.P. Levy et al. / Contraception 89 (2014) 431-433

Take-Home

- Evidence from more than 5000 women during product development, and 1.4 million women in EC postmarketing surveillance indicates that the use of UPA 30 mg for EC appears safe.

- When a copper IUD can’t be placed within 5 days, improving women’s access to ulipristal acetate for EC is important given its efficacy and safety profile (including for Ms Whoopsy Daisy).

- Using the most effective method is especially important for overweight and obese women¹,²

What’s new with Cervical Cancer Screening?

HPV Primary Screening?

• ATHENA trial evaluated HPV test as primary screen for cervical cancer in women ≥25 years old
• HPV alone detected more cases of CIN3+ but required more colposcopies
• Promising but not currently recommended as a primary screening test
  • ATHENA, 2015
Key Article


Self-collected vaginal HPV testing
• provides sensitivity and specificity comparable to clinician-collected specimens
• is more sensitive than cytology

The News

Use of Primary High-Risk Human Papillomavirus Testing for Cervical Cancer Screening: Interim Clinical Guidelines
• Huh WK et al. Obstet Gynecol Feb 2015

• Sponsored by the Society of Gynecologic Oncology and ASCCP
• Representatives also from ACOG, ACS, ASC, CAP, ASCP
Interim Guidelines

- Primary hrHPV screening
  - *can be considered as an alternative* to current U.S. cytology-based cervical cancer screening methods
  - should occur *no sooner than every 3 years*
  - *should not be initiated before 25 years* of age
- The panel had concerns about harms.
  “Progression to cancer is uncommon, and detection of most of the disease found in the 25-29 year age group can be safely deferred until age 30 and older.”
- Based on limited evidence, *this triage approach appears reasonable*:

**Recommended primary HPV screening algorithm**

(NILM= negative for intraepithelial lesion or malignancy)
*If ≥ ASC-US or persistent hrHPV => colpo*

Primary hrHPV Screening Interim Guidance. Obstet Gynecol 2015
Screening Guidelines

- Cobas HPV test is approved for primary screening for women ≥25
- These interim guidelines have not been adopted by other organizations such as the USPSTF and the ACS or ACOG
- Critiques that these recommendations may be premature
- Primary HPV screening may have a role in resource limited settings

Screening Pelvic Examination?

- A part of preventive health care for women for many years
- Not needed for contraception or STD screening
- What is the goal of a screening pelvic examination?
Screening Pelvic Examination: ACP Evidence Report

• Systematic review of 52 studies
• No evidence supporting the use of pelvic examination in asymptomatic average risk women
  • May cause pain, discomfort, fear, anxiety and embarrassment in about 30% of young women

Screening Pelvic Examination?

• Diagnostic accuracy for detecting ovarian cancer or BV is low
• Rarely detects non-cervical cancer or other treatable conditions
• ACP recommends against performing screening pelvic examination in asymptomatic, non-pregnant adult women
  • (strong recommendation, moderate-quality evidence)

• ACOG acknowledges that no current scientific evidence supports or refutes an annual pelvic exam for an asymptomatic, low-risk patient; however, continues to firmly believe in the clinical value of pelvic examinations.²

² Ann Intern Med. 2014;161:67-72
² ACOG. Advisory on Annual Examination Recommendations 2014
Impact for practice

- Clinicians who choose to perform pelvic examinations in asymptomatic women should be aware that there is uncertain benefit and there is the potential to cause harm through a positive test result and subsequent testing.
Vasomotor Symptoms

- Minnie Pause is a 53 year old woman who had her last menstrual period 18 months ago. She is still having hot flashes and awakens at least twice a night with them. She is considering taking estrogen but wants to know how much longer this will last. What do you tell her?
What do you tell her about when they will go away?

- Average duration is about 2 years and so they should be gone in about 6 months.
- Average duration is about 4 years
- Average duration is about 7 years
- They will never go away

Background

- Treatment for menopausal symptoms is based on their transitory nature
- Many clinical guidelines suggest that symptom duration is approximately 2 years
  - Many studies do not follow women more than 2 years
- Risks and benefits of hormone therapy depend on duration of use
  - “Use lowest dose for shortest duration”
The News

- **Duration of Menopausal Vasomotor Symptoms Over the Menopausal Transition**

- **Objectives**
  - To determine:
    - Total duration of frequent vasomotor symptoms (VMS) during the menopausal transition (frequent = > 6 days/2 weeks)
    - How long frequent VMS persist after the final menstrual period (FMP)
    - Risk factors for longer total VMS duration and longer post-FMP persistence
SWAN Study

- Multi-ethnic, multi-racial observational study of menopausal transition in 3302 women at 7 sites
  - 13 visits over 17 years
  - Analyses of 1449 women with frequent VMS
  - Assessed VMS duration and persistence after FMP

Results

- Median duration of VMS was 7.4 years
  - FMP persistence 4.5 years
- Longer VMS duration in women who were pre or perimenopausal when symptoms began
  - Median 11.8 years
- Women who were postmenopausal when symptoms began had shortest duration
  - Median 3.4 years
- Longer VMS duration
  - African American, younger age, lower educational level, greater perceived stress and symptom sensitivity and higher depressive symptoms and anxiety
Results

- Risk factors
  - Perceived stress
  - Higher symptom sensitivity
  - Lower educational level
  - More anxiety

- No association with physical activity or alcohol intake

Impact

- Frequent VMS lasted more than 7 years for more than half of women
- The earlier VMS started the longer they were likely to last
- VMS duration and post-FMP persistence varied by race/ethnicity
  - African American women had the longest duration and persistence
  - Chinese and Japanese women had the shortest duration and persistence
- This can be included in decision making about menopausal symptom management
Minnie Pause (continued)

• Ms. Pause is distressed to learn that her hot flashes and night sweats may persist for several more years. She has been dealing with them for long enough and if they aren’t going to stop soon she wants to do something about them. She is afraid to take estrogen because she is worried about her heart and breast health. One of her friends takes a “psych medication” for her hot flashes, but Ms. M. Pause worries that it might not work for her. What do you recommend?

What do you recommend?

• For her hot flash treatment she should...
  • A. Avoid SSRI or SNRI therapy because it only works in women who have been menopausal for many years (>5 years).
  • B. Consider SSRI or SNRI therapy because recent evidence indicates that it may be as effective as low-dose estrogen therapy.
  • C. Avoid SSRI or SNRI therapy because it only works in women who are depressed or anxious.
  • D. Take a placebo pill, because it is just as effective as an SSRI or SNRI.
What do you recommend?

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  • D. Take a placebo pill, because it is just as effective as an SSRI or SNRI.

The News

• Randomized Controlled Trial of Low-Dose Estradiol and the SNRI Venlafaxine for Vasomotor Symptoms

• Objectives:
  • To determine the efficacy of estrogen therapy and venlafaxine, relative to placebo, for reducing VMS
Methods

- **Population**
  - Women ages 40-62 years in the late menopausal transition (amenorrhea >60 days in past year) or postmenopausal
  - > 14 VMS/week
- **Intervention**
  - Estrogen therapy: 17-β estradiol 0.5mg/day
  - Venlafaxine: 75mg/day
- **Comparison**
  - Placebo
- **Outcome**
  - VMS frequency
- **Trial design**
  - Randomized, double-blinded
  - Follow-up for 8 weeks

Results

- 339 women randomized
  - 59.9% White, 34.2% African American, 5.9% Other/Unknown
  - 15.3% Perimenopausal, 75.5% Postmenopausal

<table>
<thead>
<tr>
<th>VMS Frequency</th>
<th>Estradiol</th>
<th>Placebo</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>8.5 (7.4, 9.7)</td>
<td>7.7 (6.9, 8.5)</td>
<td>0.9 (-0.5, 2.2)</td>
</tr>
<tr>
<td>Week 8 - baseline</td>
<td>-4.5 (-5.4, -3.6)</td>
<td>-1.9 (-2.8, -1.6)</td>
<td>-2.3 (-3.4, -1.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VMS Frequency</th>
<th>Venlafaxine</th>
<th>Placebo</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>8.2 (7.1, 9.3)</td>
<td>7.7 (6.9, 8.5)</td>
<td>0.5 (-0.8, 1.8)</td>
</tr>
<tr>
<td>Week 8 - baseline</td>
<td>-3.9 (-4.7, -3.1)</td>
<td>-2.2 (-2.8, -1.6)</td>
<td>-1.8 (-2.7, -0.8)</td>
</tr>
</tbody>
</table>
Results

- **Comparative efficacy: reduction in VMS**
  - Estradiol: 53%
  - Venlafaxine: 48%
  - Placebo: 29%

- **Adverse events**
  - No significant difference among groups
  - Venlafaxine: more women with htn (12)
  - Estradiol: more women with AUB (6)

Estradiol reduced VMS frequency by an additional 0.6VMS/day relative to venlafaxine

No interaction effects with race, menopause status, VMS duration, anxiety, depression, perceived stress

Conclusions

- Both low-dose estrogen therapy and venlafaxine are significantly more effective than placebo for reducing VMS
  - 32% greater reduction with estradiol
  - 20% greater reduction with venlafaxine

- There are relatively minor differences in efficacy between low-dose estrogen therapy and venlafaxine

- Adverse events are uncommon and consistent with known side effects for each therapy
Take Home

• This is the first trial to simultaneously investigate the efficacy of low-dose estrogen and an SNRI for treatment of VMS.

• Venlafaxine compares favorably to low-dose estrogen in this study, but it is unclear how it would compare to standard-dose estrogen.

• Since M. Pause is concerned about adverse effects associated with any dose of estrogen, venlafaxine may be a good choice for her, and she may have a 50% reduction in hot flashes during the first 8 weeks.
Bone Health

Case

• Bonnie Bony is a 76 year old woman who has been on alendronate for 5 years. You started it for a hip BMD 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 needs to worry about ONJ. What do you tell her?
What do you tell Bonnie?

A. ONJ only occurs in people on IV bisphosphonates for cancer

B. You should be fine as long as you aren’t planning any dental procedures

C. The risk will increase the longer you take alendronate

Potential Long-term Side Effect of Bisphosphonates?
Background

- Previous studies have shown an association between ONJ and high dose bisphosphonates used in oncology
- Association with lower doses used for osteoporosis has been less clear
  - Prior estimates were between 1/10,000 to 1/100,000
- Prior retrospective study suggested a possible increased risk in Asian Americans

The News

- *The risk of osteonecrosis of the jaws in Taiwanese osteoporotic patients treated with oral alendronate or raloxifene*
  - Chiu et al, J Clin Endocrinol Metab 2014
- Aims:
  - To evaluate whether oral bisphosphonates in doses used for osteoporosis prevention are associated with an increased risk of ONJ compared with raloxifene
  - To evaluate potential contributing factors that may be important in an Asian population
Methods

- Women aged 50 and over and men aged 60 and older who began taking alendronate between 2000 and 2012
  - Retrospective pharmacy database
  - Compared with women age 50 and over taking raloxifene
- Antiresorptive-related ONJ
  - Presence of exposed bone in maxillofacial region for more than 8 weeks in persons treated with alendronate or raloxifene without jaw radiotherapy
  - Hospital claims codes and record reviews

Results

- 7332 patients for analysis
  - 40 alendronate related ONJ cases
  - 22 had invasive dental procedures before developing ONJ
- Overall incidence of ONJ over 12 years: 0.55%
  - 0.25% for two years
  - 6.0% for 10 years
- Attributable risk associated with alendronate
  - 283 per 100,000 patient years
## Results: ONJ Risk Factors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adjusted OR</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 65-80 vs &lt;65</td>
<td>4.14</td>
<td>(1.24-13.89)</td>
</tr>
<tr>
<td>Age ≥80 vs &lt;65</td>
<td>5.65</td>
<td>(1.57-20.38)</td>
</tr>
<tr>
<td>Duration ≥3 years vs &lt;3 years</td>
<td>5.73</td>
<td>(2.97-11.04)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>2.00</td>
<td>(1.04-3.87)</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>4.56</td>
<td>(1.73-12.07)</td>
</tr>
</tbody>
</table>

## Conclusions

- Oral bisphosphonates when used for osteoporosis therapy are associated with ONJ
- The risk increases with duration of use
- Risk is increased with increasing age and in women with diabetes and rheumatoid arthritis
Take-Home

- Decision making about duration of bisphosphonate use is complex and ONJ risk should be one factor to consider
- The risk is highest in older women, who have been on therapy for a longer duration and who have diabetes or rheumatoid arthritis
- Back to Bonnie: Although the absolute risk is relatively low, her age and co-existing diabetes put her at higher than average risk of ONJ which may be a factor in her decision-making

Bonnie Bony continued

- After discussing ONJ risk with you, Bonnie is now trying to decide whether or not to stop the alendronate. She is worrying about having a fracture if she stops the alendronate. She wants to know what tests you can do to help determine her risk if she stops the medication. What do you tell her?
  We can check:
  A. a DXA now and three years after you stop it
  B. bone biomarkers (NTX and BAP) now and in a year
  C. a DXA and bone biomarkers now and a year after you stop it
  D. A DXA now
The News

Fracture risk prediction after discontinuation of 4-5 years of alendronate therapy: the FLEX study.
Bauer et al. JAMA Int Med 2014

- Objective
  - To test the utility of dual-energy x-ray absorptiometry (DXA) and bone turnover marker measurements at the time of discontinuation and after 1 to 3 years of follow-up for 5-year fracture risk prediction among women who have discontinued alendronate after previously being treated with it for 4-5 years

Methods

- 1099 women were enrolled in the Fracture Intervention Trial Long Term Extension (FLEX)
  - Randomized to receive alendronate (5-10 mg) or placebo after 4-5 years of alendronate
  - Analysis of 437 participants assigned to the placebo group
- DXA of hip and spine measured at baseline
  - Hip BMD repeated annually
  - Spine BMD at 36 months
- Bone turnover markers measured at baseline, 12 months and 36 months
  - Bone specific alkaline phosphatase (serum)
  - Urinary N-telopeptide (NTX)
- Self reported fractures confirmed by radiology or central reports
Results

- 94 of 437 women (22%) had one or more symptomatic fractures
  - Women with fracture were older (76.2 vs 73.1 years: p<0.001)
  - Women with fracture with lower hip BMD at baseline
- 82 of them had fractures after one year
  - 12 had fractures before one year DXA and BTM were repeated and were excluded from primary analysis

Results: Baseline Predictors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fracture Risk (hazard ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per 5 year increase</td>
<td><strong>1.54 (1.26-1.85)</strong></td>
</tr>
<tr>
<td>BMI per SD increase</td>
<td><strong>1.10 (0.87-1.38)</strong></td>
</tr>
<tr>
<td>Vertebral fracture</td>
<td><strong>1.11 (0.72-1.75)</strong></td>
</tr>
<tr>
<td>Previous non-spine fracture</td>
<td><strong>1.24 (0.64-2.40)</strong></td>
</tr>
<tr>
<td>BMD lowest tertile vs other Total hip*</td>
<td><strong>1.87 (1.2-2.92)</strong></td>
</tr>
<tr>
<td>BMD lowest tertile vs other Femoral neck*</td>
<td><strong>2.17 (1.38-3.41)</strong></td>
</tr>
<tr>
<td>BTMs highest tertile vs other NTX/Cr (nmol/mmol)</td>
<td>1.33 (0.84-2.10)</td>
</tr>
<tr>
<td>BTMs highest tertile vs other NBAP (ng/ml)</td>
<td>1.39 (0.89-2.17)</td>
</tr>
</tbody>
</table>

*Lowest tertile for hip was -2.3 to -4.2 and lowest tertile for femoral neck was -2.5 to -4.1.
Results: Changes in BMD and BTMs

- The majority of associations between 2 and 3 year changes in BMD and fracture risk were not significant
  - Two year total hip bone loss greater than 3% was significantly associated with fracture risk (HR 1.68 (95% C.I. 1.05-2.72)
    - 3 year change was not significant
  - Neither 2 or 3 year change in femoral neck BMD nor 3 year change in spine BMD was associated with fracture risk
  - Three year changes in BTMs after discontinuation of alendronate were not associated with fracture risk

Conclusions

- Older age and lower hip DXA at time of discontinuation of alendronate are related to an increased fracture risk in the subsequent 5 years
- One year changes in DXA, NTX and BAP were not related to subsequent fracture risk
- Three year changes in NTX and BAP were not related to subsequent fracture risk
- Women with the most bone loss after 2-3 years may be at increased fracture risk
Take-Home

- Follow up DXA one year after discontinuation of alendronate is *not* recommended
- Follow up measurements of BAP and NTX 1-2 years after discontinuation of alendronate is not recommended
- Decision making regarding discontinuation of alendronate therapy should include age and BMD at time of discontinuation

Bonnie’s next question

- Bonnie is going to schedule her DXA scan and discuss the options with you after she does. However, she wants to know whether or not you are going to check her Vitamin D level. 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. Yes, we should check your Vitamin D level since you have osteoporosis.
  D. I don’t know. What do you want to do?
Vitamin D

- Vitamin D is clearly associated with bone health, although less clearly associated with other outcomes
- IOM recommends
  - 600 IU daily of Vitamin D daily for most adults
  - 800 IU of Vitamin D daily for individuals aged 71 and over
- Should we screen or ensure adequate intake for all?

USPSTF: Vitamin D Screening Recommendations

- The USPSTF concludes that there is insufficient evidence to recommend for or against Vitamin D screening for community dwelling, non-pregnant asymptomatic adults aged >18.
  - Grade I recommendation
- USPSTF does recommend Vitamin D supplementation to prevent falls in community dwelling adults who are high risk for falls
  - Exercise and physical therapy are recommended also
  - Grade B recommendation
Back to Bonnie?

- Are you going to check her Vitamin D level?
- Given that she already has osteoporosis and you are trying to ensure optimal bone health, it would probably be reasonable.

Breast Health
Case

Maggie Mamm is 52 and she calls to schedule her screening mammogram. The scheduler asks if she’d like to try tomosynthesis instead of standard mammography.

Which is true of tomosynthesis?

A. It doesn’t require compression  
B. It uses less radiation than a standard mammogram  
C. It decreases the chance of being called back for a follow up mammogram  
D. Guidelines recommend its use for dense breasts

Tomosynthesis (aka 3D Mammography):
• Images acquired simultaneously with conventional digital mammography. X-ray source moves in an arc.
Background

- Computerized reconstruction into thin slices to minimize the influence of overlapping breast structures
- Makes invasive cancers more conspicuous while reducing false positive results
- Doubles the total radiation dose, but still well below the limits defined by the FDA
- FDA approved in 2011 to be used in combination with digital mammography for screening

http://investors.hologic.com/
The News

*Breast Cancer Screening Using Tomosynthesis in Combination with Digital Mammography*


Objectives: Determine if mammography combined with tomosynthesis is associated with better performance of breast cancer screening programs in the US

- Recall rate for additional imaging
- Cancer detection rate
- Positive predictive value for recall
- Positive predictive value for biopsy

Methods

- Retrospective analysis
- 13 academic and non-academic breast centers in US
- Mean age 57 years
- Period 1: One year before (281,187 mammograms)
- Period 2: After implementation (173,663 mammograms)

Center X

<table>
<thead>
<tr>
<th>Standard</th>
<th>Standard + tomosynthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete vs hybrid implementation</td>
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</table>
## Results

<table>
<thead>
<tr>
<th></th>
<th>Standard Digital Mammography</th>
<th>Standard + Tomosynthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Per 1000 screens (model adjusted)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recalls</td>
<td>107</td>
<td>91</td>
</tr>
<tr>
<td>Biopsies</td>
<td>18.1</td>
<td>19.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Cancer detected</strong></td>
<td></td>
<td></td>
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<tr>
<td>Invasive</td>
<td>2.9</td>
<td>4.1</td>
</tr>
<tr>
<td>In situ</td>
<td>1.4</td>
<td>1.4</td>
</tr>
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Results

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<tr>
<td>Cancer detected</td>
<td>4.2</td>
<td>5.4</td>
</tr>
<tr>
<td>Invasive</td>
<td>2.9</td>
<td>4.1</td>
</tr>
<tr>
<td>In situ</td>
<td>1.4</td>
<td>1.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Positive predictive value (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Recalled for imaging</td>
<td>4.3</td>
<td>6.4</td>
</tr>
<tr>
<td>Biopsy</td>
<td>24.2</td>
<td>29.2</td>
</tr>
</tbody>
</table>

All differences were statistically significant p<0.01

Conclusions

• Limitations: Non-randomized, lack of long term follow up information, no data on clinical outcomes
• Addition of tomosynthesis to digital mammography was associated with a decrease in recall rate and increase in cancer detection rate
• Further studies are needed to assess the relationship to clinical outcomes
Take-Home

• Confirms results of smaller studies in the US and Europe
• Tomosynthesis is likely an advance over digital mammography for screening
• Debate continues about whether/how much screening saves lives without undue false positives and over-diagnoses and whether some screen-detected cancers could be managed more conservatively

Back to Maggie

Maggie Mamm is a 52 year old woman who calls to schedule her screening mammogram. The scheduler asks if she’d like to try tomosynthesis instead of standard mammography.

Which is true of tomosynthesis?

A. It doesn’t require compression  
B. It uses less radiation than a standard mammogram  
C. It decreases the chance of being called back for a follow up mammogram  
D. Guidelines recommend its use for dense breasts
Anything else?

• Suzie Scholar has patiently listened to lectures at Advances In Internal Medicine for two days......she wonders if there is anything more that is related to women’s health......

Guidelines Updates 2015

• Duration of tamoxifen in women who have had breast cancer
• AHA Stroke Prevention Guidelines
Tamoxifen and Breast Cancer

- Women diagnosed with hormone receptor-positive breast cancer who are pre/perimenopausal should be offered adjuvant endocrine therapy with tamoxifen for 5 years. After that,
  - If premenopausal, offer treatment with tamoxifen for an additional 5 years
  - If postmenopausal, offer tamoxifen or AI for total duration of up to 10 years
- Women who are postmenopausal and intolerant of either tamoxifen or an AI should be offered the alternative type of adjuvant endocrine therapy
  - Up to 5 years of the alternative therapy
    - ASCO Guidelines 2014

Stroke Prevention in Women: AHA 2014 Guideline Highlights

- For atrial fibrillation, use risk stratification tools that account for age and sex specific differences in stroke incidence
  - CHA$_2$DS$_2$-VASc
- Migraine headache with aura
  - Reducing headache frequency is a possible strategy for stroke reduction
  - Caution women about the use of OCPs
- Absolute risk associated with OCPs is low
  - Identify women with risk factors
  - No routine screening for prothrombotic mutations and biomarkers
- Hormone therapy associated with increased risk of stroke
- Consider ASA in women >65 if BP controlled and benefits outweigh risk of GI bleeding
- Pregnancy
  - Document pre-eclampsia as a risk factor
  - Consider treating women with hypertension (SBP 150-159 or DBP 100-109) during pregnancy
Ms Whoopsy Daisy cont...

After your prescribe her EC, you ask Ms Daisy why she was only relying on condoms for her contraception. She notes that though she was happy with her OC regimen (20 mcg ethinyl estradiol/drospirenone 3 mg), she discontinued it after seeing legal ads on Facebook. She had previously tried multiple other OCs which she did not tolerate. You discuss more effective long acting reversible contraceptives (LARCs) with her, but she is not interested in an IUD or an arm implant at this time. You suggest she:

A. restart her prior OC regimen (20mg EE/DRSP 3 mg)
B. retry some other OCs, since there are so many of them
C. try trusting her doctor of many years instead of some legal ad
Background

- DRSP products approved for contraception, acne and PMDD
  - Spironolactone derivative
- FDA mandated new package insert that VTE risk *may* be increased
- $1.575 billion settlements in the US

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VTE Risk with DRSP relative to LNG containing OCs (adjusted risk)

![Graph showing VTE risk comparison](image-url)
The News

- *Cardiovascular and general safety of a 24-day regimen of drospirenone-containing combined oral contraceptives: final results from the International Active Surveillance Study of Women Taking Oral Contraceptives*
  - Dinger et al. Contraception 2014

- **Objective:**
  - Investigate short and long term risks of an extended 24-day regimen of drospirenone (DRSP_{24d}) and ethinyl estradiol compared to established oral contraceptives (OCs)

Methods

- Safety study requested by the FDA and the European Medicines Agency
- **Study Design:**
  - Prospective, controlled, noninterventional cohort study
  - 2285 study centers in the US and 6 European countries
  - Baseline health and CV risks data recorded on a questionnaire
- **Main cohorts:**
  - users of DRSP_{24d} (24-day regimens of DRSP-containing OCs), DRSP_{21d}, non-DRSP OC, and levonorgestrel (LNG) OC
- **Outcomes of interest:** VTE, arterial thromboembolism (ATE), serious adverse events (SAE)
Results:

- 85,109 women followed for 4-6 years; ~3% lost to follow up
- All OC cohorts (including LNG) showed similar incidence rates for VTE, ATE, SAE, death, cancer and depression
- ATE were low (per 10,000 WY):
  - DRSP24d: 1.5
  - DRSP21d: 1.8
  - non-DRSP: 2.8
  - LNG: 3.6
  - non-user: 1.4
- Those who stopped all OC had higher rate of SAE
  - SAEs typically in connection with pregnancy, delivery
    - Rate ratio for nonuse vs DRSP24d: 1.84

Results:

VTE, absolute risks

<table>
<thead>
<tr>
<th>VTE</th>
<th>(Sub)Cohort</th>
<th>Incidence (events/10,000 WY)</th>
<th>HR (DRSP24d vs. comparators)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Point estimate</td>
<td>95% CI</td>
</tr>
<tr>
<td>Confirmed</td>
<td>DRSP24d</td>
<td>7.2</td>
<td>4.3–11.2</td>
</tr>
<tr>
<td></td>
<td>Non-DRSP</td>
<td>9.6</td>
<td>7.8–11.6</td>
</tr>
<tr>
<td></td>
<td>LNG</td>
<td>9.8</td>
<td>5.9–15.2</td>
</tr>
</tbody>
</table>
Take-Home

- A 21 or 24 day regimen of 20 mcg ethinyl estradiol and drospirenone 3 mg was associated with similar risks to other OCs

- Ms Daisy should be encouraged to go back on the DRSP pills that have worked for her in the past

- She should be counseled that an unintended pregnancy will increase her risk of both ATE and VTE events far more than any contraceptive.

*Remember:* Breast/pelvic exams, STI screening, mammography or Pap tests are not needed prior to initiating/refilling hormonal contraceptives! ¹

¹CDC. Selected Practice Recommendations (SPR); MMWR 2013.

Case

Your 20 year old patient is past due for her third dose of the Gardasil HPV vaccine. You’ve heard there is a new 9-valent HPV vaccine coming out soon and wonder if she should wait and get that one, instead, for her third dose. She is sexually active and has had two partners in her lifetime.

What percentage of cervical cancer is targeted by the new 9-valent HPV vaccine?

A. 70%
B. 80%
C. 90%
D. 100%
Your 20 year old patient is past due for her third dose of the Gardasil HPV vaccine. You’ve heard there is a new 9-valent HPV vaccine coming out soon and wonder if she should wait and get the third dose of that one, instead. She is sexually active and has had two partners in her lifetime.

What percentage of cervical cancer is targeted by the new 9-valent HPV vaccine?

A. 70% Old Gardasil
B. 80%
C. 90% New Gardasil 9
D. 100%
The News

A 9-Valent HPV Vaccine Against Infection and Intraepithelial Neoplasia in Women

- Joura et al. NEJM 372;8 (Feb 2015)

Objective:
- Compare the new Gardasil 9 to the “old” 4-valent Gardasil vaccine in women 16-26 years of age

Methods

- Double-blind RCT in 14,000 women
- Randomized to new vs old vaccine
- Pap smear and swabs for HPV at baseline and every 6 months x 4.5 years
- Abnormal pap-> colposcopy
Methods

1. **Intention-to-treat population**
   - Received at least one dose
   - Had at least one measurement of efficacy

2. **Per-protocol, susceptible population**
   - Negative for the 5 additional HPV subtypes
   - Received all 3 doses within 1 year
   - No protocol violations

Results

- **Susceptible population:**
  - New vaccine was 96.7% effective for preventing CIN2+ from the *five additional subtypes*

- **Intention to treat population:**
  - CIN2+ related to *any* HPV subtypes:
    - Old vaccine: 14/1000
    - New vaccine: 14/1000  ➔ **No difference** (equally effective)
    - HPV negative at baseline: 2.4/1000 vs 4.2/1000  ➔ **New vaccine a little better**
Conclusions

• 9-valent HPV vaccine extends the coverage of the quadrivalent vaccine in preventing high grade dysplasia
  • All three doses
  • Given prior to HPV exposure

Take-Home

• 9-valent HPV vaccine could replace the quadrivalent vaccine
• FDA approved Dec 2014
  • females ages 9-26 and males ages 9-15
  • Available soon. $$$
• Vaccinate early, before exposure to HPV
  • CDC, AAP: Routinely immunize 11-12 year olds
• Back to our 20 year old patient due for her 3rd shot
  • Probably best to go ahead and finish the quadrivalent series