

Update in Women's Health

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Issues for Reproductive Age Women

Pelin Batur, MD, CCD, NCMP

Case

- Mrs S.R. is a 27-year-old female who presents for her annual, including her cervical cancer screening. Several years ago she had two miscarriages at 25 weeks gestation, and is hoping to try to conceive again. At that time, antiphospholipid antibody testing was negative. She has read that aspirin may improve her chances of getting pregnant, and asks you for advice. When you encourage her to discuss this with an obstetrician, she notes that because of a newer high deductible plan, she would like to avoid an OB visit until she actually becomes pregnant. At this time you:
 - A. Advise against any pharmacologic therapy
 - B. Recommend she start 81 mg aspirin daily
 - C. Recommend she start 81 mg aspirin and heparin
 - D. More strongly (yet kindly) encourage her to discuss this with an OB

The News

- *Preconception low-dose aspirin and pregnancy outcomes: results from the EAGeR randomised trial*
 - Schisterman et al. Lancet 2014;384:29-36
- Objective:
 - In women with one or two pregnancy losses, does daily 81 mg aspirin (initiated preconception) improve the likelihood of live birth?

Methods

- Study Design: Multi-center, randomized, double-blind, placebo-controlled trial
- Participants: Women aged 18-40 years, from 4 US university medical centers
 - *Original stratum*: women with 1 loss at < 20 wks gestation in the past year
 - *Expanded stratum*: 1-2 previous losses, no restrictions on gestational age or time of loss
- Inclusion criteria: Trying to conceive & regular menstrual cycles in the last yr (q 21-42 days)
- Exclusion criteria:
 - Major medical problems
 - History of infertility
 - Contraindication to aspirin
 - Indication for anticoagulant treatment

Results: Primary Outcome

- No significant difference in live birth rates, except in the original stratum (1 loss, <20 wks gestation, during the previous year)
 - 151 live births in the low-dose aspirin group
 - 133 live births in the placebo group
 - RR 1.17 (1.01 to 1.37)

Conclusions

- Overall, preconception 81 mg asa treatment does not increase the rate of live births or reduce the rate of pregnancy loss in women with a history of 1-2 previous pregnancy losses.
- Treatment might increase pregnancy rates in women with a single recent loss.
 - Further research is needed
 - Should not be recommended until findings confirmed
- Aspirin was not associated with any increase in adverse events.
 - Caution advised given patients were higher socioeconomic status and no major birth defects seen (as compared to expected population norms)

Take-Home

- Our patient should be advised that aspirin unlikely to help
 - Her history is 2 losses, yrs ago, >20 wks
- This adds to current evidence to date showing that aspirin is NOT helpful in increasing live birth rate in those:
 - undergoing IVF
 - or women with recurrent (>2) pregnancy loss
 - both with and without antiphospholipid syndrome
- Women with antiphospholipid antibodies may benefit from a combination of combined unfractionated heparin and aspirin treatment

Hmmmmm.... Wasn't there a recent USPSTF guideline about aspirin use in young women...

??????

USPSTF Guideline

- **Recommends** the use of low-dose asa (81 mg/d) after 12 weeks of gestation in women at high risk for preeclampsia (B recommendation)
 - ↓preeclampsia by 24%
 - ↓risk for preterm birth by 14%
 - ↓risk of IUGR by 20%
- Does not increase risks (ie placental abruption, postpartum hemorrhage, or fetal intracranial bleeding)
- No developmental harms identified by 18 months of age
 - 1 study reviewed
 - Evidence on long-term outcomes in offspring limited

USPSTF Guideline

<u>Recommend</u> asa if ≥ 1 high-risk factors	<u>Consider</u> asa if several moderate-risk factors
history of preeclampsia	nulliparity
multifetal gestation	obesity
chronic hypertension	mother or sister with preeclampsia
type 1 or 2 DM	African American race
renal disease	low socioeconomic status
autoimmune disease (i.e., SLE, antiphospholipid syndrome)	low birthweight
<p>ACOG recommends only for PMH of:</p> <ol style="list-style-type: none"> 1. early onset preeclampsia and preterm delivery (<34 weeks) or 2. preeclampsia > 1 previous pregnancy 	age $\geq 35y$
	previous adverse pregnancy outcome
	10-y pregnancy interval

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

1. Noé G, et al. Contraception 2011; 84:486–492.

2. Novikova N, et al. Contraception 2007; 75:112–118.

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)
 - Except for one case of fainting, all others were assessed as unlikely to be related to UPA use:
 - viral infection
 - transient hemianopsia (10 days after intake in a 33-year-old with thrombophilia and several other risk factors for thrombosis)
 - stroke 4 months after drug intake
 - severe malaise attributed to acute allergy
 - seizure in an epileptic
 - ruptured ovarian cyst

Take-Home

- Data from more than 5000 women during product development, and 1.4 million women in EC postmarketing surveillance indicate 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 methods is especially important for overweight and obese women^{1,2}

1. Glasier et al. Contraception 2011; 84(4):363-7.

2. Kapp et al. Contraception 2015;91(2):97-104.

Ms Whoopsy Daisy cont...

After you 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 her facebook page warning her of dangers of this med. 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 and PMDD
 - Spironolactone derivative
- FDA mandated new package insert that VTE risk *may* be increased
- \$1.575 billion settlements in the US¹

¹Bayer HealthCare stockholder newsletter, financial report as of September 30, 2013. Page 65, product related litigations.

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 DRSP24d (24-day regimens of DRSP-containing OCs) , DRSP21d, 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

Progestin Type	HR for VTE*
Drosperinone 24 d	Ref
Non-drosperinone	0.8 (0.5-1.3)
Levonorgestrel	0.5-1.6 (0.4-1.6)

*Adjusted for age, BMI, family history of thrombophilia

Conclusions

- A 21 or 24 day regimen of 20 mcg ethinyl estradiol and drospirenone 3 mg was associated with similar risks to other OCs
 - including those with a more favorable VTE profile such as LNG OCs
- Observational study, potential for bias or residual confounding exists. Cannot exclude small relative risks.
 - Though not a randomized trial:
 - was prospective
 - controlled for confounders
 - had low loss to follow up
 - study population was representative of OC users under routine clinical conditions

Take-Home

- Ms Daisy should be encouraged to go back on the DRSP pills that have worked for her in the past, so that she does not increase her risk of unintended pregnancy.
- 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.

ACP: Pelvic Exam Guideline

- **Methods:** Systematic review of evidence between 1946-2014.
- **Outcomes studied:**
 - Detection of ovarian (or other) cancer, BV, PID
 - Harms, including overdiagnosis, overtreatment, procedure-related harms (fear, anxiety, embarrassment, pain)
- **Recommendation¹:** recommends against performing screening pelvic examination in asymptomatic, nonpregnant, 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

¹Ann Intern Med. 2014;161:67-72.

²ACOG. Advisory on Annual Examination Recommendations 2014

What's new with HPV?

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University of Washington School of Medicine

VA Puget Sound Health Care System

Case

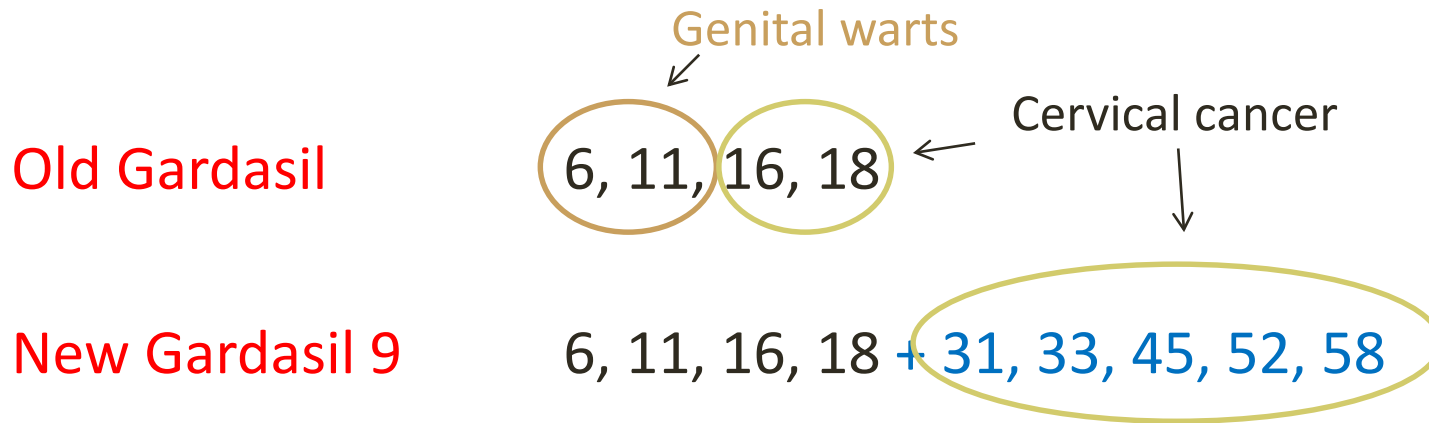
www.sheknows.com

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%

Case



Case

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

- A. 70% ← Old Gardasil
- B. 80%
- C. 90%
- D. 100%

Background

- HPV causes genital warts, and malignant lesions of the
 - Cervix
 - Vagina
 - Vulva
 - Anus
 - Penis
 - Oropharynx
- Countries with established HPV vaccination programs have found decreased high grade dysplasia

The News

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

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

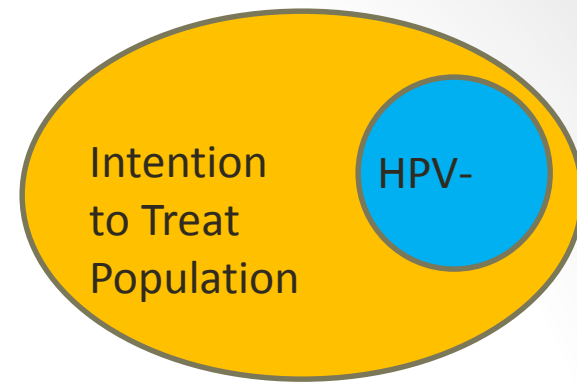
Objective:

- Compare the efficacy and immunogenicity of the new Gardasil 9 to the “old” Gardasil vaccine in women 16-26 years of age

Methods

- International double-blind RCT in 14,000 women
- Eligible women:
 - ≤ 4 lifetime partners
 - No h/o abnormal pap smear
- Randomized to **new vs old vaccine**
 - Day 1 and at months 2 and 6
- Pap smear and swabs for HPV done at baseline and every 6 months x 4.5 years
- Abnormal pap-> colposcopy

Methods



1. Intention-to-treat population

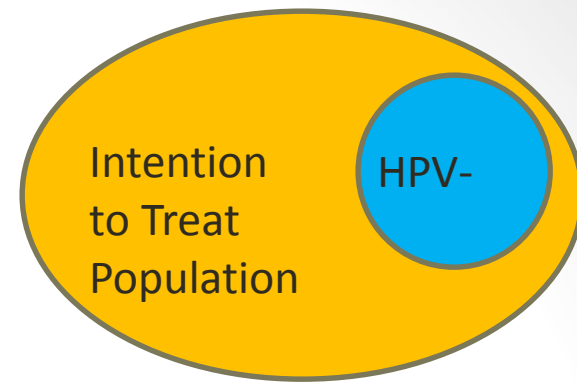
- Received at least one dose
- Had at least one measurement of efficacy

2. Per-protocol, susceptible population

- Negative for the 5 new HPV subtypes
- Received all 3 doses within 1 year
- No protocol violations

Outcome: CIN2+ = CIN2, CIN3 or adenocarcinoma in situ

Results



- **Susceptible population:**

- CIN2+ related to 5 new HPV subtypes:
 - Old vaccine: 1.6/1000
 - New vaccine: 0.1/1000
- *So new vaccine 96.7% effective for these subtypes*

- **Intention to treat population:**

- CIN2+ related to any HPV subtypes:
 - Old vaccine: 14/1000
 - New vaccine: 14/1000
 - HPV negative at baseline: 2.4/1000 vs 4.2/1000
 - So vaccinate when young – before exposed!
- More local adverse symptoms related to injection: 90 vs 85%

No difference
(equally effective)



New vaccine better

Conclusions

- 9-valent HPV vaccine extends the coverage of the quadrivalent vaccine and prevents more high grade dysplasia
- The effect of vaccination on the burden of cancer remains to be determined

Take-Home

- 9-valent HPV vaccine could replace the quadrivalent vaccine
- FDA approved in Dec 2014
 - females ages 9-26 and males ages 9-15
 - Available soon. \$\$\$
- Vaccinate early, before exposure to HPV
 - CDC, ACIP, AAP: Routinely immunize 11-12 year olds
- Problem: In the US, only 57% of girls age 13-17 have received at least one dose
- Back to our 20 year old patient due for her 3rd shot
 - Probably best to go ahead and finish the quadrivalent series

Case

You practice in a clinic that prides itself in providing “cutting edge” care. You heard the FDA approved the Roche cobas high risk HPV test for use as the primary screening test for cervical cancer. You screen a 30 year old woman with this HPV test. Which is correct about follow up?

1. If she is positive for any high risk HPV type, she should be referred for colposcopy
2. If her test is positive for HPV 16 or 18, she should be referred for colposcopy
3. If her test is positive for high risk HPV but types 16 and 18 are negative, she should be re-screened in 3 years

The News

Primary cervical cancer screening with human papillomavirus: End of study results from the ATHENA study using HPV as the first-line screening test

- Wright TC et al. Gynecologic Oncology 136 (2015) 189-197.

Objective:

To compare the performance of three cervical cancer screening strategies in women 25 years and older

Methods

42,000 women age ≥ 25 years. Three screening protocols tested simultaneously:

1. Pap smear every 3 years
2. Pap smear every 3 years (age 25-29) then co-testing (30+)
3. Primary HPV testing using this triage protocol:

Baseline
Pap
HPV



Age

25	26	27	28	29	30	31	32	33	34	35	etc
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Baseline
Pap
HPV



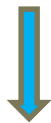
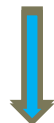
Baseline

Pap
HPV

Pap
HPV

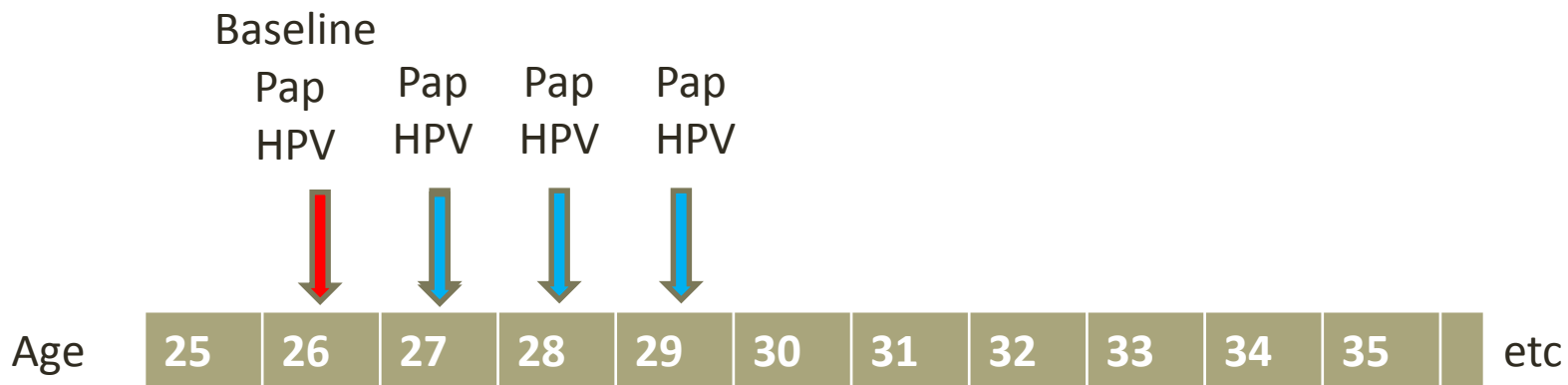
Pap
HPV

Pap
HPV

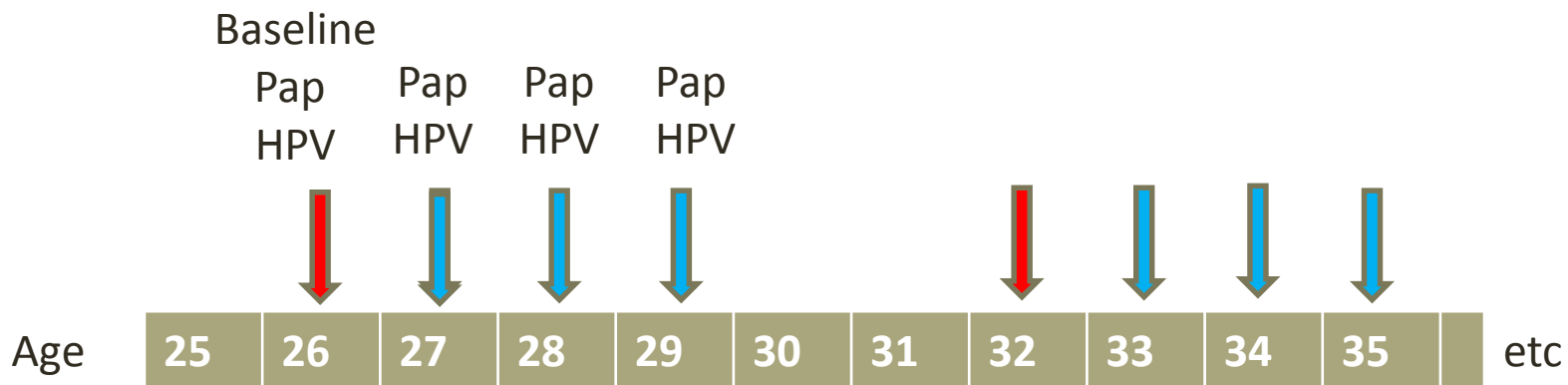


Age

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How much of the
CIN3+ was detected
by the baseline
screening test?



How much of the
CIN3+ was detected
by the baseline
screening test?

Results

- Over 3 years:
 - 319 CIN3, 20 carcinoma *in situ*, 8 invasive cancers were found

To detect CIN3+	Sens	Spec
• Paps smears	47.8%	97.1
• Paps (25-29) cotest (30+)	61.7%	94.6
• Primary HPV testing	76.1%	93.5

Increased sensitivity is due to addition of HPV at age 30

Increased sensitivity is due to starting at 25 vs 30

- Primary HPV testing resulted in many more colposcopies
- but the number of colpos to detect one case of CIN3 was similar to hybrid (about 13)

Results

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Increased sensitivity is due to starting at 25 vs 30

- Primary HPV testing resulted in many more colposcopies
- but the number of colpos to detect one case of CIN3 was similar to hybrid (about 13)

Conclusions

- Primary HPV screening at age 25+ is more sensitive than hybrid strategy to detect CIN3+
- Cytology still needs to be collected for triage
- The cytology portion of co-testing improves sensitivity only minimally for detecting CIN3+ compared to primary HPV screening
- Limitations of this study:
 - Only tested one round of screening, not comparing actual programs
 - Only one type of HPV test was evaluated
 - Underpowered to use cervical cancer as the endpoint

Take-Home

- Unknown whether detecting cases earlier (age 25 vs 30) impacts morbidity or mortality
- Optimal frequency of screening unknown
- Cost-effectiveness studies needed
- **To achieve maximum benefit of screening we need to continue to identify women who are either unscreened or under-screened**

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

Guidelines

- Primary hrHPV screening **can be considered as an alternative** to current U.S. cytology-based cervical cancer screening methods
- Rescreening after a negative primary hrHPV screen should occur ***no sooner than every 3 years***
- Primary hrHPV screening **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 years age group can be safely deferred until age 30 and older.”
- Based on limited data, **this triage approach appears reasonable:**

Back to the case...

You practice in a clinic that prides itself in providing “cutting edge” care. You heard the FDA approved the Roche cobas high risk HPV test for use as the primary screening test for cervical cancer. You screen a 30 year old woman with this HPV test. Which is correct about follow up?

1. If she is positive for any high risk HPV type, she should be referred for colposcopy
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3. If her test is positive for high risk HPV, but types 16 and 18 are negative, she should be re-screened in 3 years

Case

A 45 year old female-to-male transgender veteran with a history of military sexual trauma has not had cervical cancer screening for several years. He has had no reassignment surgery. He says he cannot tolerate a pelvic exam. He can't recall whether he has had abnormal paps, but knows that he did have a few pap smears when serving in the military. You should:

1. Skip cervical cancer screening because he is low risk
2. Schedule a pelvic exam and prescribe lorazepam 1 mg to take PO 30 minutes before the procedure
3. Test for high-risk HPV by vaginal swab
4. Test for high-risk HPV by urine sample

The News

Accuracy of urinary human papillomavirus testing for presence of cervical HPV: Systemic review and meta-analysis

- Pathak N. BMJ Vol 349. Sept 2014.

Objective:

Systematic review and meta-analysis to determine the accuracy of detection of HPV in urine compared with the cervix in sexually active women

Methods

- Meta-analysis: 14 studies
 - N=1443 women
 - Reference standard: cervical sample taken by a clinician to test for HPV DNA
 - Urine HPV – most used commercial PCR methods on first void urine samples

Results

	Sensitivity (%)	95% CI (%)	Specificity (%)	95% CI (%)
Any HPV	87	78-92	94	82-98
High risk HPV	77	68-84	88	58-97
HPV 16 or 18	73	56-86	98	91-100

Conclusions

- Very promising for non-invasive, easily accessible screening
- Lack of standardized methodology
- First-void specimen had the highest sensitivity
- Need studies on CIN/cervical cancer prediction

Case

A 45 year old female-to-male transgender veteran with a history of military sexual trauma has not had cervical cancer screening for several years. He has had no reassignment surgery. He says he cannot tolerate a pelvic exam. He's can't recall whether he has had abnormal paps, but knows that he did have a few pap smears when serving in the military. You should:

1. Skip cervical cancer screening because he is low risk
2. Schedule a pelvic exam and prescribe lorazepam 1 mg to take PO 30 minutes before the procedure
3. Test for high-risk HPV by vaginal swab
4. Test for high-risk HPV by urine sample **Not yet available**

Self-collected vaginal HPV testing provides sensitivity and specificity comparable with clinician-collected specimens, and is more sensitive than cytology.

Performance of Self-Collected Cervical Samples in Screening for Future Precancer Using Human Papillomavirus DNA Testing.

Porras C et al. JNCI J Natl Cancer Inst (2015) 107

Menopause

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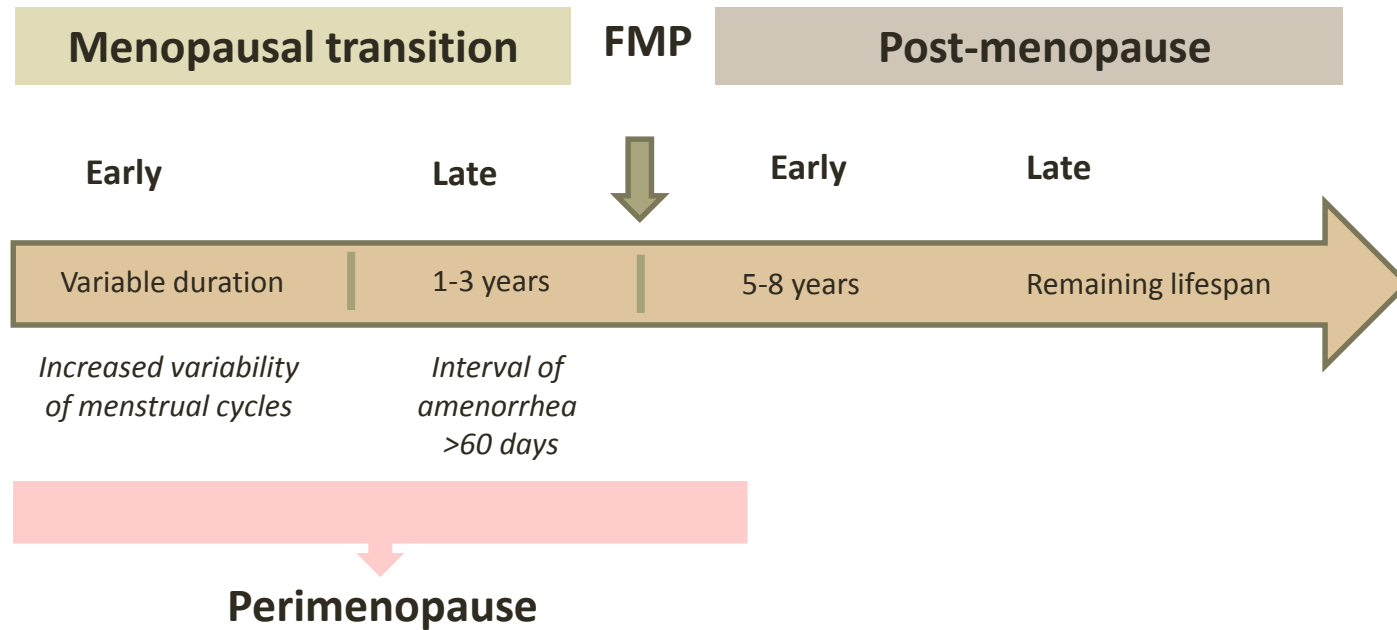
Case

- Ms. L.M. is a 53 year old female who is experiencing frequent and severe hot flashes and night sweats. Her symptoms began about 3 years ago, when she initially began to have irregular menses. She started hormone therapy two years ago with dramatic relief, but stopped it because of health concerns. Her hot flashes are really interfering with her life but she is willing to “tough it out” if you think that they will get better. What do you tell her?
 - A. Hot flashes typically last for about 2 years after the last menses, so they should stop soon.
 - B. Since she started having hot flashes several years ago, before her menses even stopped, they should stop soon.
 - C. Women with frequent, severe hot flashes (as compared to mild hot flashes) tend to have less prolonged symptoms, so they should stop soon.
 - D. She should consider treatment, since her hot flashes may persist for a decade or more.

The News

- *Duration of Menopausal Vasomotor Symptoms Over the Menopausal Transition*
 - Avis et al. *JAMA Intern Med.* 2015
- Study 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

Background



Methods

3302 women:
baseline cohort

SWAN: Multiracial/multiethnic observational study from 1996-2013
Age between 42-52
Menstrual cycle in the last 3 months

1853 Excluded

1149 women:
VMS duration
sample

Outcome #1: Years elapsed between
first and last report of frequent VMS

First report of VMS

Last report of VMS

568 Excluded

881 women:
Post-FMP persistence
sample

Outcome #2: Years elapsed between first
and last report of frequent VMS after FMP

FMP

First report of VMS

Last report of VMS

Results

- Median total duration of VMS: 7.4 years
- Median post-FMP persistence: 4.5 years
- Both VMS duration and post-FMP persistence were longer with earlier symptom onset and among African-American women

Results

- Risk factors
 - Perceived stress
 - Higher symptom sensitivity
 - Lower educational level
 - More anxiety
- No association with physical activity or alcohol intake

Conclusions

- Women who experience VMS at an earlier menopausal stage (premenopause or early perimenopause) have longer VMS duration (11.8 years) and post-FMP persistence (median 9.4 years)
- 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
- Although menopausal transition stage is the best predictor of VMS duration and post-FMP persistence, anxiety and stress may also play a role

Take-Home

- This article adds to the body of evidence that many women experience frequent VMS for several years (much longer than the 6 months- 2 years listed in current guidelines)
- Women like Ms. L.M., who experience symptoms in early perimenopause, may have frequent VMS for 11 years or more, and can consider medical therapy to improve quality of life
- Current guidelines for hormonal therapy recommend the lowest dose for the shortest duration – thus we have limited evidence directing us how to manage long-term VMS

Ms. L.M.'s Case (continued)

- Ms. L.M. 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 felt "great" on estrogen therapy but is worried about her heart and breast health. One of her friends takes a "psych medication" for her hot flashes, but Ms. L.M. worries that it might not work for her. 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. Avoid SSRI or SNRI therapy because it only works in women who are depressed or anxious.
 - C. Take a placebo pill, because it is just as effective as an SSRI or SNRI.
 - D. Consider SSRI or SNRI therapy because recent evidence indicates that it may be as effective as low-dose estrogen therapy.

The News

- *Randomized Controlled Trial of Low-Dose Estradiol and the SNRI Venlafaxine for Vasomotor Symptoms*
 - Joffe et al. *JAMA Intern Med* 2014; 174(7): 1058-1066.
- Study 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

VMS Frequency	Estradiol	Placebo	Difference
Baseline	8.5 (7.4, 9.7)	7.7 (6.9, 8.5)	0.9 (-0.5, 2.2)
Week 8 - baseline	-4.5 (-5.4, -3.6)	-1.9 (-2.8, -1.6)	-2.3 (-3.4, -1.3)

VMS Frequency	Venlafaxine	Placebo	Difference
Baseline	8.2 (7.1, 9.3)	7.7 (6.9, 8.5)	0.5 (-0.8, 1.8)
Week 8 - baseline	-3.9 (-4.7, -3.1)	-2.2 (-2.8, -1.6)	-1.8 (-2.7, -0.8)

Results

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

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

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

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

Conclusions

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

Key Article

- *Effects of Low-Dose Paroxetine 7.5mg on Weight and Sexual Function During Treatment of Vasomotor Symptoms Associated with Menopause*
 - Portman et al. *Menopause* 2014; 21(10): 1082-1090.
- Analysis of pooled data from the two phase 3 studies that demonstrated the efficacy of paroxetine 7.5mg for the treatment of VMS
- At 24 weeks:
 - No significant differences in % weight change from baseline in the treatment and placebo groups (paroxetine +0.48% vs. placebo +0.09%)
 - No significant differences in proportion of women reporting sexual dysfunction in treatment and placebo groups (56% vs. 57%)

Case

- Ms. K.M. is a 42 year old female presenting for routine follow-up. She had a TAHBSO at age 36 for treatment of endometriosis and has been on topical estrogen therapy since that time. She has recently been feeling more sluggish and fatigued, and has had a more difficult time completing her work-outs as an avid cyclist. She is sexually active and does not have significant concerns, although wonders if she could be “in the mood” a bit more. She wonders if her testosterone is low, and if so, whether she would benefit from testosterone therapy. What do you tell her about testosterone therapy?
 - A. It is associated with significant adverse effects in women and should be avoided.
 - B. It is unlikely to improve her fatigue and sense of well-being.
 - C. It has been shown to help with all types of sexual dysfunction.
 - D. It may help improve her sex life and muscle strength.

The News

- Testosterone Dose-Response Relationships in Hysterectomized Women With or Without Oophorectomy: Effects on Sexual Function, Body Composition, Muscle Performance and Physical Function in a Randomized Trial
 - Huang et al. *Menopause* 2014; 21(6) 612-623.
- Study Objective:
 - To determine, *among androgen-deficient women*, whether improvements in sexual function, muscle mass and performance, and physical function can be achieved at testosterone concentrations that do not produce significant androgenic adverse effects

Background

- Trials of testosterone therapy for the treatment of sexual dysfunction have produced conflicting results
 - Multiple studies showed benefit with testosterone patch treatment among women with HSDD and natural or surgical menopause
 - However, two phase III trials of testosterone gel failed to show benefit
- Lack of data regarding the effects of testosterone on body composition, muscle performance, and physical function

Methods

- Multicenter, double-blind, randomized trial
- Women ages 21-60 with hysterectomy +/- partial or total oophorectomy
 - Serum total T < 31ng/dL or free T < 3.5 pg/mL
 - FSH > 30 units/L



Run-in period:
50µg of estradiol via
patch

Treatment period:
Weekly injections of placebo or testosterone
Placebo: n = 15
3mg/week: n = 14
6.25mg/week: n = 14
12.5mg/week: n = 15
25mg/week: n = 13

Primary outcome
Change from baseline score -
Brief Index of Sexual
Functioning for Women

Secondary outcomes
Changes in:
Lean body mass
Fat mass
Voluntary muscle strength
Muscle power
Physical function
Psychological general well-
being

Results

- 25mg group (*only*):
 - Significant changes in sexual thoughts/desire and frequency of sexual activity as compared to placebo group
 - Mean increase of 2.7 sexual encounters/week, associated with higher free T concentrations (supraphysiologic)
 - No changes in relationship satisfaction, receptivity/initiation, pleasure/orgasm

Results

- ***Secondary outcomes***

- Significant increases in lean body mass (1.8kg), chest-press power, and loaded stair-climb power among women in the 25mg group
- No changes in gait speed, lift and reach, unloaded stair climb speed
- Improvement in psychological general well-being (12.5 and 25mg groups)

- ***Adverse events***

- Small but significant increases in Ferriman-Gallwey score in 12.5mg, 25mg groups as compared to placebo
- Dose-dependent increases in hemoglobin and hematocrit
- No clitoromegaly

Conclusions

- Among androgen-deficient women without sexual dysfunction at baseline, supraphysiologic concentrations of injectable testosterone are associated with:
 - Increased sexual activity and sexual thoughts/desire
 - Increased LBM and strength
 - Few adverse effects
- Limitations
 - Small study – no benefits seen at *physiologic* testosterone doses, but perhaps underpowered?
 - Short duration – unclear if adverse effects would increase or accumulate with time
 - Co-intervention – estrogen administration may have mitigated adverse effects of T on lipids

Take Home

- This study showed limited benefit of testosterone injections at *physiologic doses* for improving sexual function or muscle mass/strength, but it may have been underpowered for this
- It is reassuring that even very high concentrations of T were associated with few adverse events
- I would be reluctant to start Ms. K.M. on injectable T therapy for improving fatigue, physical function, or sexual function until additional data are available

Key Article

Androgen Therapy in Women: A Reappraisal: An Endocrine Society Clinical Practice Guideline

RECOMMENDS FOR:

- Treatment of postmenopausal women with HSDD
 - High physiological doses of testosterone therapy for 3-6 months
 - Endogenous testosterone levels do not predict response to therapy
 - No preparations are currently FDA-approved in the United States
 - No safety and efficacy data are available after 24 months of therapy

RECOMMENDS AGAINST:

- Making a clinical diagnosis of androgen deficiency syndrome in healthy women, as data correlating androgen levels with specific symptoms/signs are lacking
- Using testosterone therapy for sexual dysfunction other than HSDD, bone health, or well-being

Bone Health

Judith Walsh, MD, MPH

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?

- ONJ only occurs in people on IV bisphosphonates for cancer
- You should be fine as long as you aren't planning any dental procedures
- The risk will increase the longer you take alendronate

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

Parameter	Adjusted OR	95% C.I.
Age 65-80 vs <65	4.14	(1.24-13.89)
Age ≥80 vs <65	5.65	(1.57-20.38)
Duration ≥3 years vs <3 years	5.73	(2.97-11.04)
Diabetes Mellitus	2.00	(1.04- 3.87)
Rheumatoid Arthritis	4.56	(1.73-12.07)

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 DXA now and three years after you stop it
- bone biomarkers (NTX and BAP) now and in a year
- a DXA and bone biomarkers now and a year after you stop it
- your bone density 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 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 : $p < 0.0001$)
 - Women with fracture with lower hip BMD at baseline
- 82 of them had fractures after one year

Results

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

*Lowest tertile for hip was -2.3 to -4.2 and lowest tertile for femoral neck was -2.5 to -4.1.

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 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?
 - Of course. We should check Vitamin D levels in everyone
 - No. Just be sure you are taking a Vitamin D supplement of 800 IU a day.
 - Yes, we should check your Vitamin D level since you have osteoporosis.
 - 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

Judith Walsh, MD, MPH

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?

1. It doesn't require compression
2. It uses less radiation than a standard mammogram
3. It decreases the chance of being called back for a follow up mammogram
4. Guidelines recommend its use for dense breasts

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

The News

Breast Cancer Screening Using Tomosynthesis in Combination with Digital Mammography

- Friedewald SM et al. JAMA 2014;311(24):2499-2507.

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

Standard



Standard +
tomosynthesis

Complete
vs hybrid
implementation

Results

	Standard Digital Mammography	Standard + Tomosynthesis
Per 1000 screens (model adjusted)		
Recalls	107	91
Biopsies	18.1	19.3
Cancer detected	4.2	5.4
Invasive	2.9	4.1
In situ	1.4	1.4

Results

	Standard Digital Mammography	Standard + Tomosynthesis
Per 1000 screens (model adjusted)		
Recalls	107	91
Biopsies	18.1	19.3
Cancer detected	4.2	5.4
Invasive	2.9	4.1
In situ	1.4	1.4
Positive predictive value (%)		
Recalled for imaging	4.3	6.4
Biopsy	24.2	29.2

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?

1. It doesn't require compression
2. It uses less radiation than a standard mammogram
3. It decreases the chance of being called back for a follow up mammogram
4. Guidelines recommend its use for dense breasts

Anything else?

- Suzie Scholar has patiently listened to this year's Women's Health Update for the past 72 minutes.....she wonders if there is anything more.....

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
 - CHA₂DS₂-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