Update in Women’s Health 2012

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Our Systematic Review

• Reviewed the literature for SGIM
  – Sonya Borrero, MD, MS
  – Jennifer McCall-Hosenfeld MD, MSc
  – Rachel Bonnema, MD, MS
• Reviewed all titles published in top journals
  – March 1, 2011 to March 1, 2012
• Evaluated potential impact on internists’ clinical practice
• Top third of abstracts reviewed by all 4 of us
• Consensus reached about those most worthy of your time today

Sources Reviewed

• New England Journal of Medicine
• Journal of the American Medical Association
• Annals of Internal Medicine
• Archives of Internal Medicine
• British Medical Journal
• Lancet
• Obstetrics and Gynecology
• American Journal of Obstetrics and Gynecology
• Journal of General Internal Medicine
• PLOS Medicine
• American Journal of Public Health
• Circulation
• Diabetes
• Cochrane database of systematic reviews
• Guideline Clearing House
• ACP Journal Club
• Journal of Women’s Health
• Journal Watch Women’s Health
• Journal Watch

Plan for today

• Cancer Screening
• Reproductive Health
• Issues for the Menopausal Woman
• Post-Menopause and Beyond
• Osteoporosis and Bone Health
The Case
Hope is a 35 year old healthy woman without medical issues who presents for her annual exam. She had been recently reading a magazine that recommended she be screened for ovarian cancer, and with a friend recently diagnosed, she wants to make sure you are screening for ovarian cancer during her pelvic. You tell her:

a. The bimanual exam is a reasonable screening test for ovarian cancer.

b. CA-125 can be sent for screening of ovarian cancer.

c. Transvaginal ultrasound can be ordered to screen for ovarian cancer.

d. Despite the media recommendation, there are no good screening tests for ovarian cancer.

Background

- Ovarian cancer is among the 5 leading causes of cancer death in women
- Extent of disease at presentation is important
  - Localized: 5-yr survival of 92%
  - Distant mets: 5-yr survival of 31%

The News

- *Effect of Screening on Ovarian Cancer Mortality: The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial*  

- Aim: Evaluate the efficacy of transvaginal ultrasound and serum CA-125 as screening tools to reduce ovarian cancer mortality

Methods

- Randomized controlled trial of 78,216 women ages 55-74
- Intervention: annual transvaginal u/s and CA-125 vs usual care
- Exclusion: previous lung, colorectal or ovarian cancer
  – Additional exclusion of current tamoxifen use dropped in 1999*
- Follow up for up to 13y from randomization

*Buys SS, et al; Am J Obstet Gynae, 2005
Methods

• Screening examination:
  ‒ 4-6 rounds of annual transvaginal u/s and CA-125
  ‒ Bimanual exam discontinued in Dec 1998
• Cancer found by screening: diagnosed as a result of investigation initiated within 9 months after positive screening test

Results

<table>
<thead>
<tr>
<th></th>
<th>Intervention (n=34,253)</th>
<th>Usual Care (n=34,304)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian CA incidence</td>
<td>212 (5.7/10,000 person yrs)</td>
<td>176 (4.7/10,000 person yrs)</td>
<td>1.21 (0.99-1.48)</td>
</tr>
<tr>
<td>Ovarian CA mortality</td>
<td>118 (3.1/10,000 person yrs)</td>
<td>100 (2.6/10,000 person yrs)</td>
<td>1.18 (0.82-1.71)</td>
</tr>
<tr>
<td>Oophorectomy</td>
<td>1771</td>
<td>1304</td>
<td>1.33 (1.24-1.43)</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>2924 (76.6/10,000 person yrs)</td>
<td>2914 (76.2/10,000 person yrs)</td>
<td>1.01 (0.96-1.06)</td>
</tr>
</tbody>
</table>

• Of 3285 False Positive results, 1080 had surgery
  • 32.9% oophorectomy
  • 15% major complication

Take Home Message

• No reduction in mortality with screening for ovarian cancer
  ‒ Among the cases detected by screening, 69% were in late stage; only slightly lower than usual care, 78%
• At this time, no benefit to screening for ovarian cancer

The Case

Janelle is a 52 year old woman who was referred to you by her friend Monique who said you were an expert with regard to cancer risk and screening. She has a strong family history of breast cancer and a personal history of menopause, DVT; after your risk assessment you find her Gail score is 2.3%. What are your recommendations regarding prevention?

a. She is a candidate for raloxifene, a SERM, given that she is postmenopausal.
b. She is a candidate for exemestane, an aromatase inhibitor, given her postmenopausal state and DVT history.
c. She is not a candidate for any chemopreventive agent.
Background

• Tamoxifen and raloxifene are both effective for chemoprevention of breast cancer
  – Tamoxifen: NNT 95 after 5 years, 56 after 10 years\(^*\)
  – Raloxifene: similar risk reduction at 5 years, retains ~76% of effectiveness at 10 years\(^†\)
  • Has had poor acceptance for chemoprevention, in part due to side effects


The News

• Exemestane for Breast-Cancer Prevention in Postmenopausal Women
  • Aim: To investigate exemestane in preventing incidence of invasive breast cancer in high risk postmenopausal women

Methods

• Industry funded, randomized, double blind, placebo-controlled trial of 4560 women
  – Ages 35 or older, postmenopausal
  – High risk for breast cancer
    • Gail score>1.66%, >age 60, prior atypical ductal/lobular hyperplasia, LCIS on breast bx or DCIS s/p mastectomy
  • Intervention: 25mg exemestane, planned duration 5 years
  • Primary outcome: incidence of invasive breast cancer

Results

<table>
<thead>
<tr>
<th></th>
<th>Exemestane (n=2285)</th>
<th>Placebo (n=2275)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive Breast CA</td>
<td>11</td>
<td>32</td>
<td>0.35 (0.18-0.70)</td>
</tr>
<tr>
<td>ER positive</td>
<td>7</td>
<td>27</td>
<td>0.27 (0.12-0.60)</td>
</tr>
<tr>
<td>ER negative</td>
<td>4</td>
<td>5</td>
<td>0.80 (0.21-2.98)</td>
</tr>
</tbody>
</table>

• NNT = 94 in 3 years, 26 in 5 years (few women completed 5 years)
Results

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Exemestane, n (%)</th>
<th>Placebo, n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any side effect</td>
<td>1963 (88%)</td>
<td>1901 (85)</td>
<td>0.003</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>900 (40)</td>
<td>718 (32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Joint pain</td>
<td>665 (30)</td>
<td>606 (27)</td>
<td>0.04</td>
</tr>
<tr>
<td>Skeletal fx</td>
<td>149 (6.7)</td>
<td>143 (6.4)</td>
<td>0.72</td>
</tr>
<tr>
<td>New osteoporosis</td>
<td>37 (1.7)</td>
<td>30 (1.3)</td>
<td>0.39</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>106 (4.7)</td>
<td>111 (4.9)</td>
<td>0.78</td>
</tr>
</tbody>
</table>

- No difference in health-related QOL on the SF-36
- Worse menopause-specific QOL in exemestane

Take Home Message

- Exemestane decreased incidence of invasive breast cancer by 65%
  - No serious adverse events were seen in this trial
- Not FDA-approved, but expect further studies

Reproductive Health

Case

Zahra is a 21 yo woman with no medical issues who is requesting birth control pills. She has many friends who are on Yasmin® and is interested in starting this method but has recently heard concerning reports about blood clots. How do you advise her?

1. There are too many risks with OCPs - she should just use condoms
2. This is true, and the FDA has pulled all drospirenone-containing OCPs off the US market
3. There is a small but apparent risk and it would be better to try a different OCP initially
4. This is not true, the media has blown the risks out of proportion and you are happy to write a prescription for her
Background

- The first OCPs introduced contained high doses of both estrogen and progestin
- High estrogen doses associated with increased risk of VTE
- In the mid-1990s, concerns about type of progestin became a focus for VTE risk
  - 3rd generation progestins (desogestrel) higher risk than 2nd generation (levonorgestrel)

The News

- Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drosperinone compared with women using oral contraceptives containing levonorgestrel: Case-control study with US claims data
  - Jick and Hernandez. BMJ. 2011

- Aim: To compare risk of VTE in women receiving drosperinone-containing OCPs versus women receiving levonorgestrel-containing OCPs

Methods

- Design: Nested case-control and cohort study using PharMetrics, a US company that collects claims information from managed care plans
- Participants: all women 15-44 who received an OCP with either drosperinone or levonorgestrel after Jan 1, 2002 until December 2008
  - Cases: women with current use of a study OCP with idiopathic VTE
  - Controls: up to 4 controls matched to each case by age and calendar time
  - Excluded women with risk factors for VTE

- Drosperinone is a 4th generation progestin that has anti-androgenic and anti-mineralocorticoid (diuretic) properties
- Heavily marketed for treatment of moderate acne and premenstrual dysphoric disorder
  - Yasmin® (with 30mg EE); generics: Ocella®, Syeda®, Zarah®
  - Yaz® (with 20mg EE); generics: Gianvi®, Loryna®
  - Safyral® and Beyaz® (Yasmin® and Yaz® with folate)
Results: Odds ratios for VTE

<table>
<thead>
<tr>
<th>Exposure</th>
<th>No (%) cases (n= 186)</th>
<th>No (%) controls (n= 681)</th>
<th>Crude OR* (95% CI)</th>
<th>Adjusted OR** (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levonorgestrel Drosperinone</td>
<td>65 (15) 121 (28)</td>
<td>368 (85) 313 (72)</td>
<td>2.3 (1.6 – 3.2)</td>
<td>2.4 (1.7 – 3.4)</td>
</tr>
<tr>
<td>Levonorgestrel 20 users only</td>
<td>20 (13) 121 (28)</td>
<td>131 (88) 313 (72)</td>
<td>2.7 (1.6 – 4.7)</td>
<td></td>
</tr>
<tr>
<td>Levonorgestrel 30 users only</td>
<td>45 (16) 121 (28)</td>
<td>237 (84) 313 (72)</td>
<td>2.1 (1.4 – 3.1)</td>
<td>2.2 (1.5 – 3.4)</td>
</tr>
</tbody>
</table>

*For overall analysis, crude OR is a conditional OR based on matched cases and controls; for stratified analyses, crude ORs are adjusted for age and year
** Also adjusted for duration of use

Results: Incidence rates and incidence rate ratios for VTE from cohort analysis

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Cases (n=186)</th>
<th>Person years</th>
<th>Incidence rate per 100,000 person years</th>
<th>IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drosperinone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;30</td>
<td>63</td>
<td>253,895</td>
<td>24.8</td>
<td>4.6 (2.6-8.2)</td>
</tr>
<tr>
<td>Age 30-39</td>
<td>42</td>
<td>107,701</td>
<td>39.0</td>
<td>2.1 (1.3 – 3.3)</td>
</tr>
<tr>
<td>Age 40-44</td>
<td>16</td>
<td>31,248</td>
<td>51.2</td>
<td>2.4 (1.2 – 4.8)</td>
</tr>
<tr>
<td>Levonorgestrel</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;30</td>
<td>14</td>
<td>259,522</td>
<td>5.4</td>
<td>ref</td>
</tr>
<tr>
<td>Age 30-39</td>
<td>35</td>
<td>187,017</td>
<td>18.7</td>
<td></td>
</tr>
<tr>
<td>Age 40-44</td>
<td>16</td>
<td>75,284</td>
<td>21.3</td>
<td></td>
</tr>
</tbody>
</table>

IRR adjusted for age = 2.8 (2.1-3.8)

Results

• Cases more likely to be obese than controls (13% vs 6%)
• Adjusting for diagnosis of obesity did not change conditional OR (2.3; 1.6-3.3)
• Drosperinone-users more likely to be younger, have a history of menstrual disorders, and be new users
• Adjustment for each of these conditions also did not change ORs

Relevant key article

Risk of venous thromboembolism in users of oral contraceptives containing drosperinone or levonorgestrel: Nested case-control study based on UK General Practice Research Database
Parkin et al. BMJ 2011

Bottom line: Current use of drospirenone was associated with a 3-fold higher risk of VTE compared with levonorgestrel use
Relevant key article

*Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9*

Lidegaard et al. BMJ 2011

Bottom line: Desogestrel, gestodene, and drospirenone carried at least 2-fold higher for VTE compared with levonorgestrel

Take home message

- Current users of OCPs containing drospirenone have an increased risk of non-fatal VTE compared with users of OCPs with levonorgestrel
- In Dec 2011, FDA advisory panel voted that the benefits of drospirenone-containing OCPs currently outweigh the risks, but that the pills’ labels should better highlight the risks of VTE

Case

Kaya is a 24 yo woman who comes to your office for a Pap smear. She says that she always has a lot of discomfort during speculum insertion and asks that you use a gel lubricant. What do you say?

a. Lubricant is only helpful for postmenopausal women
b. You cannot use lubricant because it will interfere with the cytology interpretation
c. Water is just as helpful for decreasing pain as a gel lubricant
d. Okay

Background

- Fear of pain is a common barrier to patient compliance for cervical cancer screening
- Wide use of lubricating gel for vaginal speculum exams hampered by beliefs that get interferes with cervical cytology and STI screening results
  - Strong RCT evidence that using gel does not increase unsatisfactory PAP testing rates or differences in Chlamydia detection rates

1 Hoyo et al.: Prev Med 2005
2 Amies et al: Obstet Gynecol 2002
3 Griffith et al.: Contraception 2005
The News

• **Effect of lubricating gel on patient comfort during vaginal speculum examination**

• Aim: To estimate whether using lubricating gel decreases patient pain during speculum insertion compared with using water

Methods

• Study design: Single-blinded RCT

• Participants: All women aged 18-50 who required a vaginal speculum exam between Feb-July 2011
  —Excluded women with conditions that may alter pain perception with speculum insertion (menopause, pregnancy, dyspareunia)

• Intervention: Insertion of a speculum prepared with either gel or water

Methods

• Procedures:
  —Single clinician
  —Standardized technique using medium-sized plastic speculum

• Outcome: Pain as assessed on a 10-cm visual analog scale (VAS)
  —assessed immediately after speculum insertion and before any other procedures
  —Reduction of 0.9cm on the VAS deemed clinically significant

Results

• A total of 229 women included; 92% for routine annual gynecologic exam

• Lower pain scores in gel group compared to water group (1.41 vs 2.15; p<.011); difference of 0.74 cm

• 33.9% of gel participants compared to 10% of water participants reported zero pain (p=0.002)
Take home message

- Applying a small amount of lubricating gel can decrease patient pain during vaginal speculum insertion

Case

You explain to Kaya that because of her age, you will also be testing for chlamydia. She interrupts to tell you that she has been in a same-sex relationship for the past year and therefore thinks she is at low risk for STIs. What do you tell her?

a. Oh good, you don’t have to screen her then
b. Actually, there is evidence that chlamydia prevalence may be higher in women who have sex with women (WSW)
c. She’s right, her risk is lower but you will screen her anyway based on current guidelines that recommend screening all women aged 24 years and younger

Background

- Chlamydia is the most common STI in the US
- CDC and USPSTF guidelines currently recommend annual screening for all women ≤ 24 years
- Relatively little is known about chlamydia acquisition among women who report exclusive same-sex sexual behavior
  - Transmission between women through the exchange of infected cervico-vaginal secretions on hands or objects (sex toys)

The News

- Chlamydia trachomatis infection among women reporting sexual activity with women screened in family planning clinics in the Pacific Northwest, 1997 to 2005
- Aim: To describe the prevalence of chlamydial infection among WSW
Methods

• Study design: Secondary data analysis
  – Data from family planning clinic visits in the Pacific Northwest from 1997 – 2005
  – Widespread/universal screening for chlamydia in family planning clinics for women aged 15-24 in this region since 1988 as part of the CDC’s Infertility Prevention Project
  – 604,616 chlamydia test records obtained in the study timeframe
  – Women asked whether they sexual intercourse in the past 12 months exclusively with women (WSW), exclusively with men (WSM), or with both men and women (WSMW)

• Outcome: Chlamydial test positivity

Results

• Of the 604,616 chlamydia test records:
  – 98.5% among WSM
  – 0.9% (n=5714 cases) among WSW
  – 0.6% (n=3644) among WSMW
  – Majority of women presenting for “routine” visit

<table>
<thead>
<tr>
<th></th>
<th>WSM</th>
<th>WSW</th>
<th>WSMW</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. Trachomatis positivity (%)</td>
<td>5.3</td>
<td>7.1</td>
<td>7.1</td>
</tr>
<tr>
<td>Crude OR and 95% CI</td>
<td>-</td>
<td>1.4 (1.2 – 1.5)</td>
<td>1.4 (1.2 – 1.6)</td>
</tr>
<tr>
<td>Adjusted OR and 95% CI</td>
<td>-</td>
<td>1.1 (0.9 – 1.2)</td>
<td>1.0 (0.9 – 1.2)</td>
</tr>
</tbody>
</table>

Take home message

• Women who report sexual activity with women are at risk for genital chlamydia infection and may benefit from screening and STI prevention practices (including barrier methods and washing sex toys)

Issues for the Menopausal Woman
The Case

• Ms. Henrietta Flash is a 46 yo F who reports that she has begun to be troubled by vasomotor disturbances. Menses are regular, but have increased by a week in interval.
• PMHx: anxiety
• “Doc, I think I can get through this, but I’m not sure how long I can put up with this. How long do you think this will go on?”

What is the likely duration of menopausal hot flushes?

a) 6 months to 2 years
b) 2 years to 5 years
c) 5 years to 10 years
d) You don’t want to know…

Background

• Clinical guidelines indicate the duration of hot flushes is 6mo-2y*
• Most prior studies examined populations of older women
• Newer data suggests that these durations might be longer when younger women are included
• Counseling regarding duration of hot flushes may inform clinical decision making


The News

• Duration of menopausal hot flushes and associated risk factors
  – Freeman, EW et al. Obstetrics and Gynecology, May 2011

• Aim: To estimate the duration of moderate-to-severe menopausal hot flushes and identify potential risk factors for hot flush duration.
Methods

- Penn Ovarian Aging Study - 436 premenopausal women, ages 35-47 years (not using hormonal therapy of any type); followed for 13 years
  - Analytic Subsample: 259 women did not report hot flushes at baseline but did experience mod/severe sx during follow-up
- Measures: validated menopausal symptom list embedded in structured interview, hormones
- Assessments made at 9-month intervals during study years 0-5, then annually until year 10, every other year until study completion

Menopausal stages

- Premenopause: regular menstrual cycles 22-35 days long
- Late premenopause: change of more than 7 days in cycle length
- Early transition: changes in cycle length of 7 days or more in either direction for 2 consecutive menstrual cycles OR 60 days amenorrhea
- Late transition: 90 d to 11 months amenorrhea
- Postmenopause: 12 months or more amenorrhea


Results

Results – Hazard Ratio for Likelihood of Hot Flashes Ending

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menopausal</td>
<td></td>
</tr>
<tr>
<td>Premenopausal or Late Premenopausal</td>
<td>Ref.</td>
</tr>
<tr>
<td>Early Transition</td>
<td>3.26 (1.78-5.97)</td>
</tr>
<tr>
<td>Late Transition or Postmenopausal</td>
<td>5.14 (2.70-9.77)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>39 or younger</td>
<td>0.33 (0.14-0.78)</td>
</tr>
<tr>
<td>40-44</td>
<td>0.52 (0.30-0.91)</td>
</tr>
<tr>
<td>45-49</td>
<td>Ref.</td>
</tr>
<tr>
<td>50 or older</td>
<td>1.00 (0.54-1.87)</td>
</tr>
<tr>
<td>White Race (Ref: African American)</td>
<td>1.73 (1.11-2.68)</td>
</tr>
<tr>
<td>BMI 30 or more (Ref: BMI under 30)</td>
<td>1.94 (1.25-3.02)</td>
</tr>
<tr>
<td>Estradiol (mean)</td>
<td>0.82 (0.64-1.05)</td>
</tr>
</tbody>
</table>

Fig. 1. Kaplan-Meier estimates of hot flush duration by menopausal stage and symptom onset. Log rank PC=0.01.
Take home message

• In this population-based cohort, median duration of moderate-to-severe hot flushes was...10.2 years!
  – Adding mild hot flushes...duration was 11.6 years
• Younger, thinner, African-American women are likely to have longer hot flush duration
• Effect of hormone therapy on hot flush duration was not evaluated
• Clinicians counseling patients about hot flash duration should be mindful that the earlier the hot flashes start, the longer they are likely to last!

The case continues...

• Henrietta Flash declines therapy for her hot flushes. “Doc, I can live with it.”
• She returns to your clinic the following year. Her hot flush symptoms are moderate, and she is very interested in starting soy.
• “Doc, I’ve heard that eating soy will help with these symptoms. It’s more natural, right? Also, my mom had osteoporosis. Can’t soy protect my bones?”

Background

• Soy products have been proposed to provide comparable benefits to estrogen for treating menopausal symptoms, without the risks
• Epidemiologic studies on Asian women suggest that soy-containing foods are of benefit to the skeleton
  – Limited by short duration, low dose of soy isoflavones, few participants
• Rapid bone loss occurs during the first 2 years of menopause

The News

• Soy isoflavones in the prevention of menopausal bone loss and menopausal symptoms.

• Aim: To determine the efficacy of soy isoflavone tablets in preventing bone loss and menopausal symptoms.
Methods

• SPARE study (Soy Phytoestrogens As Replacement Estrogen) – parallel group, placebo controlled, double blind trial
• 248 women (early menopause) were randomly assigned to receive 200mg soy isoflavones or placebo
• Measures:
  – BMD change
  – Vaginal Maturation
  – Lipids and thyrotropin
  – Assessed at baseline, 12 mo, & 24 mo

Results at year 2

• No significant differences between soy and placebo group:
  – Spinal BMD
  – Total hip BMD
  – Femoral neck BMD
  – NTx (N-telopeptide type I bone collagen)
• Subgroup analyses by: race, BMI, estradiol, 25-OH Vit D
  – Women with low 25-OH vit D at baseline – soy group had lower decrease in spinal BMD than placebo

What about other menopausal symptoms?

<table>
<thead>
<tr>
<th></th>
<th>Soy Isoflavone</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flashes</td>
<td>48.4%</td>
<td>31.7%</td>
<td>.02</td>
</tr>
</tbody>
</table>

• No difference
  • vaginal maturation values (VMVs)
  • change in cholesterol or triglyceride levels
  • thyrotropin levels

• Adverse events:
  • Constipation marginally higher in the soy group (31%) vs. placebo (21%), p=.06

Take home message

• This was an overweight, calcium-replete group – rate of bone loss was slower
  – Overall low rates of bone loss (2.3% L Spine); 2.1% femoral neck) may have prevented detection of treatment effect
• Soy isoflavones (200 mg qd) did not prevent bone loss or reduce menopausal symptoms
• Hot flushes more common in the soy group, suggesting an antagonistic effect
• Clinical message: no evidence that soy isoflavones are effective in preventing bone loss
Post-Menopause and Beyond

Case

- Polly P is a 65 year old woman who notes increasing pelvic pressure and urinary urgency from her prolapsed uterus. She has met with her gynecologist and has decided to have a hysterectomy. She wants your opinion on whether or not she should have her ovaries removed at the time of surgery.

What is your advice?

- Of course they should be removed—that is what we always do for postmenopausal women
- Leave them in—it is more natural
- Hmmm…..I am not sure…..what did your gynecologist recommend?

Background

- Hysterectomy is the most common non-obstetric major surgery among U.S. women
  - 90% for benign conditions
  - Elective bilateral salpingo-oophorectomy (BSO) is routinely offered to women aged 40 and over at the time of hysterectomy
- Recent controversy about oophorectomy or ovarian conservation in postmenopausal women
Background

• BSO significantly reduces ovarian cancer risk
• Some observational studies have shown an increased risk of CHD after BSO
• Some studies suggested an increased fracture risk after BSO but other studies did not confirm
• Statistical and methodologic limitations of prior studies

The News

• Oophorectomy vs ovarian conservation with hysterectomy: cardiovascular disease, hip fracture and cancer in the WHI observational study
• AIM: To examine the effect of BSO on cardiovascular disease, hip fracture and cancer

Methods

• Participants were women in the WHI Observational Study who had a hysterectomy
  – N=39,149
  – N=25,448 after excluding those with unknown oophorectomy status, oophorectomy during study or history of cancer
  – All had detailed histories of HT use
• Primary outcomes: Incident CVD, stroke and total CVD
• Secondary outcomes: X-ray confirmed hip fracture, cancer, total mortality
• Cox proportional hazards regression analyses to assess association between BSO and all outcomes

Results

• 14,254 women had BSO and 11,194 had TAH alone
  – Mean age 63, majority white with annual income >$20K
  – No differences in body mass smoking or exercise
• Mean follow-up 7.6 years
• No differences in family history of CHD, breast cancer, CRC or fracture
• Over three quarters had used HT (78.6%)
  – Majority used estrogen alone
Results in women with BSO

<table>
<thead>
<tr>
<th>Disease</th>
<th>TAH alone Number/ PYE</th>
<th>TAH-BSO Number/ PYE</th>
<th>Hazard Ratio (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal/nonfatal CHD</td>
<td>353</td>
<td>380</td>
<td>1.00 (0.85-1.18)</td>
</tr>
<tr>
<td>Stroke</td>
<td>311</td>
<td>320</td>
<td>1.04 (0.87, 1.24)</td>
</tr>
<tr>
<td>Hip Fracture</td>
<td>155</td>
<td>122</td>
<td>0.83 (0.63-1.10)</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>44</td>
<td>3</td>
<td>Unable to calculate</td>
</tr>
<tr>
<td>Total Mortality</td>
<td>1819</td>
<td>1282</td>
<td>0.99 (0.80, 1.23)</td>
</tr>
</tbody>
</table>

NNT to prevent one case of ovarian cancer: 323

Results: Subgroup Analyses

• Among women who never used HT, BSO not associated with CHD, stroke or death
• Major reduction in ovarian cancer in BSO group
• No between group differences for breast, colorectal, lung or total cancer
  – Decreased risk of breast cancer in women <40 at time of BSO
    – HR 0.36 (0.14, 0.95)

Take Home Message

• Among postmenopausal women who are undergoing hysterectomy, there do not appear to be any benefits associated with ovarian preservation.

OSTEOPOROSIS AND BONE HEALTH
Case

• Bonnie Bony is a 67 year old woman with hypertension and osteopenia comes in for an annual examination. As you review her medications with her, she tells you that she has stopped taking her calcium supplements because she heard that calcium might cause heart attacks. What do you tell her?

Choices

a) Keep taking your calcium- it’s good for your bones
b) As long as you are taking Vitamin D with it, it should be fine
c) Good decision. Stay off the calcium. Just be sure you are drinking a lot of milk.

Background

• Calcium supplements are widely recommended for bone health
• Previous studies have shown that calcium is necessary but not sufficient for reducing osteoporosis risk
• A 5 year randomized controlled trial in healthy older women, where CVD outcomes were prespecified showed possible increases in MI and cardiovascular events in women who took calcium

– Bolland MI et al. BMJ 2008

Background: 2010 Meta-analysis

• 15 eligible trials
• Calcium supplements were associated with a 30% increase in myocardial infarction and smaller, non-significant increases in stroke and mortality
  – MI risk was higher in those with a dietary calcium intake above the mean
• Findings consistent across trials
• Did not include calcium co-administered with Vitamin D
  – Bolland M et al. BMJ 2010
The News

- Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women’s Health Initiative limited access database and meta-analysis – Bolland MJ et al. BMJ 2011

- AIM: To evaluate the effects of personal calcium supplementation on cardiovascular risk in the WHI Calcium/Vitamin D supplementation study

Background

- WHI reported no adverse CVD events in 7 year RCT of calcium/vitamin D supplementation – N=36,282
- 54% of participants were taking calcium on their own and 47% were taking vitamin D
- What were the comparison groups?
- Did personal use of calcium/vitamin D obscure an adverse effect on CVD risk?

Methods

- WHI participants taking personal calcium and those not taking it were analyzed separately
- WHI outcomes analyzed separately for each group
- Meta-analysis updated to include WHI women not taking personal calcium

Results: WHI Subgroups

- 16,718 women not taking personal calcium at baseline
  - Hazard Ratio MI 1.22 (1.00 to 1.50)
  - Other individual outcomes not significant
- 19,564 taking calcium at baseline
  - HR MI 0.92 (0.75 to 1.13)
Results: Meta-analysis

- 20,090 participants from three trials of calcium plus vitamin D vs placebo
  - Two trials not published before previous meta-analysis and WHI Ca/D
  - Increased risk of MI with Ca/D
    - RR 1.21 (1.01 to 1.44)
  - Increased risk of stroke with Ca/D
    - RR 1.20 (1.00 to 1.43)

Results: Meta-analysis

- Calcium with or without Vitamin D vs placebo
  - Trial level data for 28,072 participants
  - Patient level data for 24,869 participants
  - Increased risk of MI
    - RR 1.24 (1.07 to 1.45)

Take Home Message

- Calcium with or without Vitamin D is associated with a small increased risk of cardiovascular events
- Limitations
  - Post hoc sub group analyses
  - WHI accounted for most of the weighting in the meta-analyses
- Calcium supplements modestly increase BMD and have a modest protective effect against fracture
- Should we reassess the role of calcium/vitamin D in osteoporosis prevention?

USPSTF Draft Recommendations June, 2012

- Evidence is insufficient to assess balance of benefits and harms
  - Vitamin D with or without calcium for cancer prevention
  - Vitamin D and calcium for primary prevention of fractures in postmenopausal women or men
  - Daily supplementation with >400 IU of Vitamin D3 and 1,000 mg of calcium for fracture prevention
- Recommends against daily supplementation with <400 IU of Vitamin D3 and 1,000 mg calcium for primary prevention of fractures in noninstitutionalized postmenopausal women
Case

• Bonnie is still not sure what she is going to do about her calcium/Vitamin D supplements. However, she does want to know when she should have her next bone mineral density test. Her last BMD was 2 years ago and showed osteopenia with a t score of -1.8. What do you tell her?

Choices

a) Let’s schedule it now
b) We should do it in 2 years
c) We should do it in 5 years
d) I have no idea...when do you want to do it?

Background

• Hip and vertebral fractures are associated with premature mortality
• Bone mineral density t score
  – Normal: BMD no lower than 1 SD below mean for young adult women
  – Osteopenia (Low bone mass): BMD 1.0-2.5 SD below the mean for young adults
  – (T=-1 to -2.5)
  – Osteoporosis: BMD more than 2.5 SD below young adult mean
  – (T<-2.5)

USPSTF Recommendations

• Screen all women age 65 and older
  – Evidence for screening is indirect
• Screen younger women whose fracture risk is equal to or greater than a 65 year old white woman who has no additional risk factors
• “Evidence is lacking about optimal intervals for repeated screening”
  – A minimum of 2 years may be needed to reliably measure a change in BMD
  – Longer intervals may be needed to improve fracture risk prediction

» USPSTF 2011
The News

- Bone-density testing interval and transition to osteoporosis in older women.
  - Gourlay et al. NEJM 2012
- Aim: To determine how the BMD testing interval relates to the timing of the transition from normal BMD or osteopenia to the development of osteoporosis before a hip or vertebral fracture occurs

Methods

- 4,597 women from the Study of Osteoporotic Fractures (SOF)
  - Aged 65 and older, population based
  - Study examinations at year 2, 6, 8, 10 and 16
- Outcome: Estimated interval for 10% of individuals to make transition from normal BMD or osteopenia to osteoporosis before a hip or clinical vertebral fracture or treatment for osteoporosis

Results

- Within each t score range, a percentage of women developed osteoporosis over 15 years
  - Normal 0.8%
    - (-1.00 or higher)
  - Mild osteopenia 4.6%
    - (-1.01 to -1.49)
  - Moderate osteopenia 20.9%
    - (-1.50 to -1.99)
  - Advanced osteopenia 62.3%
    - (-2.00 to -2.49)

Results/Competing Risk Analyses

- Adjusted interval between baseline testing and the development of osteoporosis in 10% of study participants
  - Normal BMD 16.8 (11.5-24.6) yrs
  - Mild osteopenia 17.3 (13.9-21.5) yrs
  - Moderate osteopenia 4.7 (4.2-5.2) yrs
  - Advanced osteopenia 1.1 (1.0-1.3) yrs
Conclusions

- Osteoporosis would develop in <10% of individuals during rescreening intervals of 15 years for women with normal BMD or mild osteopenia, 5 years for women with moderate osteopenia and 1 year for women with advanced osteopenia.

- Future screening recommendations will probably be based on likelihood of osteoporosis progression based on initial BMD.

Take Home Message

- Decisions about when to rescreen should be based on the results of initial screening.
- Few women with normal BMD will develop osteoporosis at 15 year follow-up.

Questions?