Advances in Women’s Health 2012: A Critical Review of the Year’s Most Important Papers

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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

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

Plan for today
- Cancer Prevention
- Reproductive Health
- Issues for the Menopausal Woman
- Post-Menopause and Beyond
- Calcium, Vitamin D and Bone Health
The Case
Janelle is a 52 year old woman who was referred to you by her friend 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.

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

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


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

Exemestane (n=2285) | Placebo (n=2275) | HR (95% CI)
--- | --- | ---
Invasive Breast CA | 11 | 32 | 0.35 (0.18-0.70)
ER positive | 7 | 27 | 0.27 (0.12-0.60)
ER negative | 4 | 5 | 0.80 (0.21-2.98)

• 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?

a. There are too many risks with OCPs - she should just use condoms
b. This is true, and the FDA has pulled all drosperinone-containing OCPs off the US market
c. There is a small but apparent risk and it would be better to try a different OCP initially
d. 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 levonorgesterel-containing OCPs

Background
• 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)
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

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>Levonorgestrel</td>
<td>65 (15)</td>
<td>368 (85)</td>
<td>2.3 (1.6 – 3.2)</td>
</tr>
<tr>
<td></td>
<td>Drosperrinone</td>
<td>121 (28)</td>
<td>313 (72)</td>
<td></td>
</tr>
<tr>
<td>Levonorgestrel 20 users only</td>
<td>Levonorgestrel</td>
<td>20 (13)</td>
<td>131 (88)</td>
<td>2.7 (1.6 – 4.7)</td>
</tr>
<tr>
<td></td>
<td>Drosperrinone</td>
<td>121 (28)</td>
<td>313 (72)</td>
<td></td>
</tr>
<tr>
<td>Levonorgestrel 30 users only</td>
<td>Levonorgestrel</td>
<td>45 (16)</td>
<td>237 (84)</td>
<td>2.1 (1.4 – 3.1)</td>
</tr>
<tr>
<td></td>
<td>Drosperrinone</td>
<td>121 (28)</td>
<td>313 (72)</td>
<td></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 drospirenone 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.1

• 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.2,3

1Hoyo 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

• 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*
  
  - Singh et al. Am J Public Health. 2010

- 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

What do you tell her?

In women with prior hysterectomy, estrogen therapy is associated with...

a. increased risk of cardiovascular disease
b. increased risk of invasive breast cancer
c. increased risk of hip fracture
d. different outcomes, depending on how old you are when you start it

Helen Flash

- Citing your encyclopedic knowledge of the medical literature, Henrietta Flash, who you are successfully treating for menopausal symptoms, has referred her sister, Helen, to see you.
- You are not surprised when the conversation turns to menopausal issues.
- Helen Flash is a 50 yo F
  - PMHx significant for TAH.
  - "Doc, I’m confused about if I should take estrogen for my health. I don’t have a uterus, but the news keeps saying different things."

Background...The WHI, again?

- The Women’s Health Initiative Estrogen-Alone Trial was a randomized, double blind, placebo controlled clinical trial.
  - Purpose was to evaluate effects of conjugated equine estrogens (CEE) on chronic disease incidence among post-menopausal women with prior hysterectomy.
  - Trial intervention stopped 1 year early (at 7.1y of follow-up) due to increase risk of stroke.
  - Treatment effects differed by age - younger women receiving CEE had lower risk of CHD, colorectal CA, and global index of chronic disease.
  - Interaction age*disease only significant for colorectal CA.

The News

- Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy.
  – LaCroix AZ et al. JAMA 2011

- Aim: to report post-intervention outcomes at mean 10.7 years of follow-up:
  A. Assess long term effects of CEE on health outcomes
  B. Determine whether health outcomes differ between intervention and postintervention periods
  C. Determine if age-specific differences persist after stopping the intervention

Results by study period (selected outcomes)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR (95% CI)</th>
<th>Outcome</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall CHD</td>
<td></td>
<td>Hip Fracture</td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>0.95 (0.78-1.15)</td>
<td>Intervention</td>
<td>0.67 (0.46-0.96)</td>
</tr>
<tr>
<td>Postintervention</td>
<td>0.97 (0.75-1.25)</td>
<td>Postintervention</td>
<td>1.27 (0.88-1.82)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.95 (0.82-1.11)</td>
<td>Overall</td>
<td>0.92 (0.71-1.18)</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td>Invasive Breast CA</td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>1.36 (1.08-1.71)</td>
<td>Intervention</td>
<td>0.79 (0.61-1.02)</td>
</tr>
<tr>
<td>Postintervention</td>
<td>0.89 (0.64-1.24)</td>
<td>Postintervention</td>
<td>0.75 (0.51-1.09)</td>
</tr>
<tr>
<td>Overall</td>
<td>1.19 (0.98-1.43)</td>
<td>Overall</td>
<td>0.77 (0.62-0.95)</td>
</tr>
<tr>
<td>All Cancer</td>
<td></td>
<td>Global Index</td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>0.94 (0.81-1.08)</td>
<td>Intervention</td>
<td>1.03 (0.93-1.14)</td>
</tr>
<tr>
<td>Postintervention</td>
<td>0.93 (0.77-1.13)</td>
<td>Postintervention</td>
<td>1.02 (0.89-1.16)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.94 (0.84-1.05)</td>
<td>Overall</td>
<td>1.03 (0.95-1.11)</td>
</tr>
</tbody>
</table>

Results by age at enrollment (selected outcomes)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR (95% CI)</th>
<th>Outcome</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall CHD</td>
<td></td>
<td>Colorectal Cancer</td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>0.59 (0.38-0.90)</td>
<td>50-59</td>
<td>0.80 (0.40-1.61)</td>
</tr>
<tr>
<td>60-69</td>
<td>1.00 (0.80-1.24)</td>
<td>60-69</td>
<td>0.90 (0.58-1.39)</td>
</tr>
<tr>
<td>70-79</td>
<td>1.06 (0.82-1.36)</td>
<td>70-79</td>
<td>1.83 (1.08-3.12)</td>
</tr>
<tr>
<td>DVT</td>
<td></td>
<td>Hip Fracture</td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>0.71 (0.40-1.26)</td>
<td>50-59</td>
<td>1.55 (0.51-4.75)</td>
</tr>
<tr>
<td>60-69</td>
<td>1.20 (0.82-1.76)</td>
<td>60-69</td>
<td>0.87 (0.57-1.35)</td>
</tr>
<tr>
<td>70-79</td>
<td>1.26 (0.79-1.99)</td>
<td>70-79</td>
<td>0.90 (0.65-1.25)</td>
</tr>
<tr>
<td>Invasive Breast Cancer</td>
<td></td>
<td>Global Index</td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>0.80 (0.53-1.19)</td>
<td>50-59</td>
<td>0.85 (0.70-1.03)</td>
</tr>
<tr>
<td>60-69</td>
<td>0.73 (0.54-1.00)</td>
<td>60-69</td>
<td>1.00 (0.89-1.13)</td>
</tr>
<tr>
<td>70-79</td>
<td>0.81 (0.53-1.23)</td>
<td>70-79</td>
<td>1.15 (1.01-1.32)</td>
</tr>
</tbody>
</table>

Take home message

- Increases in stroke and VTE and protective effect on hip with CEE dissipated during long-term follow-up
- Lower incidence of breast CA in CEE group became significant with extended follow-up
  – Differs from preponderance (but not all) evidence
- Statistically significant age interactions for CEE group
  – greater safety and benefit for women in 50s
  – potential harm among older women
- Clinicians should counsel women differently based on age and hysterectomy status
A new clinical case

- Henrietta and Helen’s older sister, Harriet, thrilled with the excellent care given to her sibs, arrives in your clinic.
- Harriet is 55, postmenopausal and without significant vasomotor symptoms, without significant PMHx.
- You are stunned when she says she’s not here to talk about menopausal symptoms but instead says, “Doc, my hair just keeps getting thinner and thinner. Is there anything I can do about it?”
- Hx: She denies sx of hypothyroidism, hyperandrogenism, or recent illness (telogen effluvium)
- PE reveals female pattern hair loss

The review

- Androgenetic alopecia can occur at any age, but is more common among postmenopausal women
- Androgenetic alopecia follows a predictable pattern, affecting men and women differently…
- Distinguish from alopecia areata, which follows a patchy pattern
- Genetics play a role, but many factors in FPHL not well elucidated

www.uptodate.com

Which therapy has the best evidence for the treatment of female pattern hair loss?

A. Minoxidil
B. Spironolactone
C. Finasteride
D. Camouflaging
E. Hair transplant
F. She should see a psychologist

The news

- Treatment of female pattern hair loss in primary care.
  – University of Texas at Austin, School of Nursing, Family Nurse Practitioner Program, 2011
- Aim: To identify treatments for female pattern hair loss in non-pregnant adult women
Methods

• Methods: Systematic Review of electronic databases.
• USPSTF guidelines used for ranking evidence
  – Quality of evidence rated on 3 point scale (good, fair, poor)
  – Strength of evidence rated on 5 classifications (A-strongly recommends, B-recommends, C-no recommendation for or against, D-recommends against, I-insufficient evidence)
• Results of 32 articles categorized and summarized

Results

<table>
<thead>
<tr>
<th>Category</th>
<th>Treatment</th>
<th>Considerations</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharma</td>
<td>Minoxidil 2%-5% topically</td>
<td>Only FDA approved</td>
<td>Grade A-B, good</td>
</tr>
<tr>
<td></td>
<td>Minoxidil+Spironolactone</td>
<td>Little evidence</td>
<td>Grade I, poor</td>
</tr>
<tr>
<td></td>
<td>Minoxidil+Finasteride</td>
<td>Not studied in women</td>
<td>Grade I, poor</td>
</tr>
<tr>
<td></td>
<td>Finasteride</td>
<td>Pregnancy cat X</td>
<td>Grade I, poor</td>
</tr>
<tr>
<td></td>
<td>Spironolactone</td>
<td>No control, side effects</td>
<td>Grade I, poor</td>
</tr>
<tr>
<td></td>
<td>Drospironolone</td>
<td>Studies of effectiveness lacking</td>
<td>Grade I, poor</td>
</tr>
<tr>
<td>Botanicals</td>
<td>Raspberry Ketone (top)</td>
<td>No standardization</td>
<td>Grade D, poor</td>
</tr>
<tr>
<td></td>
<td>Procyanidin B-2 (top)</td>
<td>No standardization</td>
<td>Grade C, fair</td>
</tr>
<tr>
<td>Cosmetics</td>
<td>Camouflaging</td>
<td>e.g., fiber thickeners, shading</td>
<td>Grade I, poor</td>
</tr>
<tr>
<td></td>
<td>Hair styling</td>
<td>e.g., lotions, tinted powders</td>
<td>Grade I, poor</td>
</tr>
<tr>
<td></td>
<td>Hair replacement or accessories</td>
<td>e.g., extensions, wigs, scarves</td>
<td>Grade I, poor</td>
</tr>
<tr>
<td>Other</td>
<td>Nutrition</td>
<td>Vitamins, protein, minerals</td>
<td>Grade I, poor</td>
</tr>
<tr>
<td></td>
<td>Counseling/Education</td>
<td>Educate patient about hair loss triggers</td>
<td>Grade I, poor</td>
</tr>
<tr>
<td></td>
<td>Psychosocial support</td>
<td>To relieve fear and anxiety over hair loss</td>
<td>Grade I, poor</td>
</tr>
<tr>
<td></td>
<td>Referral to surgical hair restoration</td>
<td>If not satisfied with primary care</td>
<td>Grade C, fair</td>
</tr>
<tr>
<td></td>
<td>Referral to laser hair restoration</td>
<td>If declines surgical option</td>
<td>Grade I, poor</td>
</tr>
</tbody>
</table>

Results (continued)

Take home message

• Minoxidil topical is the only FDA recommended treatment for FPHL
• Data on other pharmacological, complementary and alternative, and adjunctive therapies are limited
• Much more study is needed
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?

A. Of course they should be removed—that is what we always do for postmenopausal women
B. Leave them in—it is more natural
C. 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.

Case

- Dottie D is a 68 year old woman who is increasing bothered by her overactive bladder symptoms. Despite minimizing her fluid intake, doing pelvic floor exercises and bladder training, she still urinates about 12 times a day. What do you advise as her next steps?
What do you advise?

A. Oxybutinin  
B. Oral estrogen  
C. Vaginal Estrogen ring  
D. Referral to a urogynecologist

The News

- Randomized trial of estradiol vaginal ring versus oral oxybutynin for the treatment of overactive bladder  
  - Nelken RS et al. Menopause. 2011

- Aim: To determine whether the ultralow dose estradiol-releasing vaginal ring is better than oral oxybutinin in postmenopausal women with overactive bladder

Background

- Overactive bladder: urinary frequency and urgency with or without urge incontinence  
- Prevalence increases with advancing age  
  - Approximately 40% of postmenopausal women have OAB
- Initial treatments: bladder retraining, pelvic floor strengthening, restriction of bladder irritants
- Medications have high rates of anti-cholinergic side effects  
  - Dry mouth, constipation  
  - High discontinuation rates

Methods

- Industry sponsored study  
- Participants postmenopausal with ten or more voids in 24 hour period measured by 72 hour voiding diary  
  - Exclusion: post void residual >50 cc, stress or mixed incontinence, gyn condition for which surgery planned, poorly controlled DM
- Oxybutynin 5 mg bid vs Estradiol vaginal ring (2 mg of 17-beta estradiol)  
- All counseled on managing fluid intake and pelvic floor exercises
- 12 week follow-up  
- Primary outcome: Change from baseline in number of daily voiding episodes
Results

• 31 participants received oxybutinin and 28 received vaginal ring
  – 5 lost to follow-up- 27 in each group for analysis
• Statistically significant reduction in number of daily voids in both groups
  – 3 in oxybutinin group and 4.5 in estradiol group
  – Difference between groups NS
• Improvement in scores on Urogenital Distress Inventory (UDI-6) and Incontinence Impact Questionnaire (IIQ-7) in both groups
• Women in oxybutinin group had more dry mouth, blurry vision and constipation
• Women in vaginal ring group had more vaginal discharge

Results

• At the end of the study, 85% of women in the vaginal ring group vs 59% of women in the oxybutynin group wanted to continue with the same therapy (p=0.035)

Take Home Message

• Vaginal estrogen ring may be an effective and well tolerated alternative to oxybutynin for women with overactive bladder
• A larger RCT will be needed to demonstrate whether or not it is equivalent to oxybutynin

CALCIUM, VITAMIN D 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 may 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 Bony still does not know what to do about her calcium supplements, but she wants to know if you could please check her Vitamin D level. What do you say?

Question: Vitamin D

A. Order a Vitamin D level
B. Don’t order a Vitamin D level because you are not sure to do with the results
C. Don’t order it but start her on a Vitamin D supplement

Background

• The role of Vitamin D in human health has received widespread attention
• Vitamin D clearly has a role in bone health but association with other health outcomes has been less clear
• 25-OH Vitamin D levels are widely ordered and deficiency widely treated

Screening for Vitamin D Deficiency

• Endocrine Society recommends screening in those “at high risk for deficiency” but do not recommend population based screening
  – At risk may include infants, pregnant women and the elderly
• Other organizations do not recommend screening
CASE

- Bonnie decides to start taking the Vitamin D supplement. What do you tell her about how much she needs?

Vitamin D

- A. 1,000 IU per day
- B. 2,000 IU per day
- C. 50,000 IU once a week
- D. 600 IU per day

Key Article

- Recent publication of new IOM guidelines for calcium and Vitamin D
  - [www.iom.edu/reports/2010/Dietary-Reference-intakes-for-Calcium-and-Vitamin-D](http://www.iom.edu/reports/2010/Dietary-Reference-intakes-for-Calcium-and-Vitamin-D)

- RDA
  - 600 IU for women aged 9-70
  - 800 IU for women over age 70
  - Upper limit 4,000 IU per day

- 25-OH Vitamin D level of 20 ng/ml is the goal

USPSTF: Vitamin D and Falls

- USPSTF recommends exercise or physical therapy and Vitamin D supplementation to prevent falls in community dwelling adults aged 65 and older who are at increased risk for falls
  - 600 IU daily for adults aged 51-70
  - 800 IU daily for adults over age 70
Conclusions

- Exemestane can reduce breast cancer risk but not yet FDA approved
  – Stay tuned
- Increased DVT risk associated with drospirenone containing OCPs
- Lubrication can improve patient comfort during speculum examination
- Screen for chlamydia infection in all age eligible sexually active women

Conclusions

- Counseling about hormone therapy should consider age and hysterectomy status
- Minoxidil topical is the only FDA approved treatment for hair loss
- Among women undergoing TAH, there is no benefit to ovarian preservation
- Vaginal estrogen ring may be a well tolerated alternative for OAB treatment

Conclusions

- Calcium with or without Vitamin D is associated with a small increased risk of cardiovascular events
- Vitamin D recommended for fall prevention in high risk adults
- Insufficient evidence about Calcium and Vitamin D supplementation and fracture

Questions?