Update in Women's Health

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Conflicts of Interest: None

Our Systematic Review

• Reviewed all titles published in top journals
  – March 1, 2012 to March 1, 2013

• 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

• Contraception
• Reproductive Health
• Menopause and Beyond
• Cancer Risk Factors and Screening
• Osteoporosis and Bone Health

Case

• Janet is a 32 year old female who presents to discuss contraceptive options. She is a visiting nurse who has an irregular schedule, so she has difficulty remembering to take medications. Although she is otherwise healthy, her occupation forces her to spend a lot of time in the car, and she feels that she could stand to "lose a few pounds." She knows that some contraceptives could increase her risk for "developing a clot" and wonders what you would recommend for her.

Contraception

Megan C. McNamara, MD, MSc
Case Western University
Hormonal Contraception and Venous Thrombosis

- Combined oral hormonal contraceptives (COCs) are associated with an increased risk for VTE and PE
  - Risk is higher with COCs that contain 3rd generation progestins (desogestrel, gestodene, drospirenone)
  - The risk of VTE in association with the Nuvaring® or OrthoEvra® patch is unclear

Methods

- National registry-based cohort study of all non-pregnant Danish women aged 15-49
- Outcomes:
  1. RR of VTE: users of non-oral hormonal contraception vs. non-users of hormonal contraception
  2. RR of VTE: users of non-oral hormonal contraception vs. users of reference COC
- Sources of data: national registry of patients (discharge diagnoses), national cause of death registry, national registry of medicinal products (filled prescriptions for contraceptives and anticoagulants)

Results: Risk for VTE

<table>
<thead>
<tr>
<th>Contraceptive Type</th>
<th>Number with VTE</th>
<th>Incidence of VTE/10,000 exposure years</th>
<th>Adjusted RR (compared to COC users)***</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Use</td>
<td>1210</td>
<td>2.05</td>
<td>1.00 (ref)</td>
<td></td>
</tr>
<tr>
<td>COC (levonorgestrel)*</td>
<td>231,675</td>
<td>144</td>
<td>1.00 (1.00-1.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>COC (norelgestone)**</td>
<td>298,566</td>
<td>135</td>
<td>1.09 (0.86-1.38)</td>
<td>0.465</td>
</tr>
<tr>
<td>Patch</td>
<td>6,178</td>
<td>6</td>
<td>2.31 (1.02-5.23)</td>
<td>0.046</td>
</tr>
<tr>
<td>Vaginal ring</td>
<td>50,334</td>
<td>38</td>
<td>1.90 (1.33-2.71)</td>
<td>0.001</td>
</tr>
<tr>
<td>Implant</td>
<td>29,497</td>
<td>5</td>
<td>0.43 (0.18-1.05)</td>
<td>0.084</td>
</tr>
<tr>
<td>Levonorgestrel IUS*</td>
<td>239,841</td>
<td>33</td>
<td>0.18 (0.12-0.26)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Levonorgestrel is a 2nd generation progestin
**Norelgestone is a 3rd generation progestin, of which the patch contains an active metabolite
***Adjusted for age, calendar year, length of contraceptive use

Conclusions

- The Nuvaring® and the OrthoEvra® patch are associated with an increased risk for VTE when compared to COCs
  - Both have been shown to increase resistance to Activated Protein C and increase Sex Hormone Binding Globulin levels
  - The patch is associated with higher serum estrogen levels
- Implanon® and the Mirena® do not increase the risk for VTE
Take Home Message

• The 2x increase in Relative Risk observed in this study translates into small increases in Absolute Risks
• 5,000 women using the Nuvaring ® and 2,500 women using the OrthoEvra ® Patch would need to switch to a levonorgestrel-containing COC to prevent one VTE in one year

Case

• Casey is a 38 year old female who presents to establish care. She has no complaints and is healthy, but she would like a refill on her combined oral contraceptive (COC) pill prescription. During your detailed history, your learn that she has a strong family history of cardiovascular disease – her mom had a debilitating stroke (CVA) at age 50 and her father had his first heart attack (MI) at age 45. Casey is worried about her risk for developing these conditions as well. Should you refill her prescription?

Do you refill Casey’s prescription?

• No. COCs will significantly increase her risk for CVA and MI. It would be safer to use condoms.
• No. You should recommend that she start on the Nuvaring® because it contains less estrogen than most COCs.
• Yes, but only if the COC contains a 3rd generation progestin because they are less “thrombogenic.”
• Yes. Her baseline risk for CVA and MI is very low and is unlikely to be substantially affected by COC use.

Hormonal Contraception and Arterial Thrombosis

• Studies which have examined the association between low-dose combined hormonal contraceptives and myocardial infarction (MI) and stroke (CVA) have produced conflicting results
• An understanding of the risk is essential given the devastating consequences of MI and CVA

The News

• Thrombotic Stroke and Myocardial Infarction with Hormonal Contraception
• Aim: To determine the risks for CVA and MI with use of hormonal contraception according to dose of estrogen, type of progestin, and route of administration (oral vs. ring vs. patch)

Methods

• National registry-based cohort study of all non-pregnant Danish women aged 15-49
• Outcomes:
  – RR for thrombotic stroke and MI: users of hormonal contraception vs. non-users of hormonal contraception
  – Thrombotic stroke defined as cerebral infarction and “cerebral apoplexy”; TIA’s not included
• Sources of data: national registry of patients (discharge diagnoses), national cause of death registry, national registry of medicinal products (filled prescriptions for contraceptives and anticoagulants)
Results: Thrombotic Stroke

<table>
<thead>
<tr>
<th>Type of Hormonal Contraception</th>
<th>Nortest</th>
<th>Norprogestine</th>
<th>Desogestrel</th>
<th>Drospirenone</th>
<th>Patch</th>
<th>Vaginal ring</th>
</tr>
</thead>
<tbody>
<tr>
<td># of events/100,000 person-years</td>
<td>22.1</td>
<td>31.2</td>
<td>21.6</td>
<td>18.1</td>
<td>8.7</td>
<td>31.4</td>
</tr>
<tr>
<td>Adjusted RR*</td>
<td>1.17 (1.40-3.15)</td>
<td>1.41 (1.34-1.48)</td>
<td>1.64 (1.24-2.13)</td>
<td>8.7</td>
<td>0.88 (0.22-3.53)</td>
<td>2.49 (1.43-4.43)</td>
</tr>
</tbody>
</table>

*Reference group = non-users of hormonal contraception (24.2 events/100,000 person-years) Relative risks adjusted for age, educational level, and use of medications for hypertension, heart disease, diabetes, and hyperlipidemia

Results: Myocardial Infarction

<table>
<thead>
<tr>
<th>Type of Hormonal Contraception</th>
<th>Nortest</th>
<th>Norprogestine</th>
<th>Desogestrel</th>
<th>Gestodene</th>
<th>Drospirenone</th>
<th>Patch</th>
<th>Vaginal ring</th>
</tr>
</thead>
<tbody>
<tr>
<td># of events/100,000 person-years</td>
<td>12.0</td>
<td>15.6</td>
<td>6.2</td>
<td>10.1</td>
<td>6.3</td>
<td>0</td>
<td>7.8</td>
</tr>
<tr>
<td>Adjusted RR*</td>
<td>2.28 (1.34-3.87)</td>
<td>2.02 (1.03-2.03)</td>
<td>1.33 (0.91-1.94)</td>
<td>2.09 (1.56-2.84)</td>
<td>1.94 (1.62-2.33)</td>
<td>1.65 (1.03-2.65)</td>
<td>0 (0.00-12.99)</td>
</tr>
</tbody>
</table>

*Reference group = non-users of hormonal contraception (13.2 events/100,000 person-years) Relative risks adjusted for age, educational level, and use of medications for hypertension, heart disease, diabetes, and hyperlipidemia

Conclusions

• Oral hormonal contraceptive users have a small increased risk for CVA (RR 1.17-2.20) and MI (1.33-2.28) compared to non-users
  – No significant differences in risk according to type of progestin
  – Slightly lower risk with 20mcg ethinyl estradiol preparations
• The vaginal ring increased the risk for CVA (RR 2.49) but not MI; there was no increased risk for CVA or MI among users of the patch or progestin-only methods

Take Home Message

• Progestin type does not seem to influence the risk for CVA or MI
• In patients at higher risk for CVA or MI, it may be prudent to:
  – choose an oral contraceptive with a 20mcg dose of ethinyl estradiol
  – avoid the vaginal ring
  – consider progestin-only contraceptive methods

What would you recommend for Jenna?

• Jenna is a 20-year old female who presents for routine care. Her 2-year old daughter and 6-month old son are with her during the visit. Jenna appears tired and overwhelmed, and emphatically states that she does not want to become pregnant again in the near future. She reports that both pregnancies occurred when she was using contraception, although she does admit that she “occasionally” forgot to take her COC, and that her vaginal ring “came out” one time without her realizing it. What would you recommend for her?
Prevention of Unintended Pregnancy

- Nearly half of all pregnancies that occur each year in the U.S. are unintended
- 11% of at-risk women are not using any contraceptive method
- Women who are young (age < 20 years), not married, or black are less likely to use contraception

The News

- Effectiveness of Long-Acting Reversible Contraception
  - Aim: To compare the effectiveness of long-acting reversible contraceptive methods (IUDs and implants) with other contraceptive methods (pills, patch, vaginal ring, and depo-provera) for preventing pregnancy in high-risk women

Methods

- Prospective cohort study of 9,256 sexually active women aged 14-45
- Subjects selected their free contraceptive method of choice
- Outcome: unintended pregnancy
- Sources of data: telephone interviews, pharmacy data, research log, and urine pregnancy testing

Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unintended Pregnancy (N = 156)</th>
<th>Number/100 participant-years</th>
<th>Adjusted HR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implant or IUD</td>
<td>21</td>
<td>0.27</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Depo-Provera</td>
<td>2</td>
<td>0.22</td>
<td>0.70 (0.16-3.03)</td>
</tr>
<tr>
<td>Pill, patch, or ring</td>
<td>133</td>
<td>4.55</td>
<td>21.84 (13.67-34.88)</td>
</tr>
<tr>
<td>Age &lt; 21</td>
<td></td>
<td>4.55</td>
<td>1.83 (1.25-2.69)</td>
</tr>
<tr>
<td>Age &gt; 21</td>
<td></td>
<td>1.00</td>
<td>1.00 (ref)</td>
</tr>
</tbody>
</table>

*HRs adjusted for age, educational level, number of previous unintended pregnancies

Take Home Message

- Women < 21 years have higher rates of unintended pregnancy and higher failure rates with the pill, patch, and ring
  >>> the implant or IUD may be better contraceptive options for this
Issues for Reproductive Aged Women

Sarah A. Tilstra, MD, MS
University of Pittsburgh

Case

- Abby is a 21 year old college female who presents to discuss 8 months of heavy menstrual bleeding. She frequently misses class on these days due to symptoms. Her labs show a ferritin of 9 ng/ml, hgb 10.8 g/dl, TVUS is normal. How would you counsel Abby about her management options for menorrhagia?

Menorrhagia

- The levonorgestrel-releasing intrauterine system (LNG-IUS) is an effective treatment for menorrhagia
- FDA approved Mirena® for menorrhagia in 2009
- Little evidence to guide decision making for menorrhagia therapy in primary care

The News

- *Levonorgestrel Intrauterine System versus Medical Therapy for Menorrhagia*
  - ECLIPSE trial
- Aim: Compare the clinical effectiveness of the LNG-IUS (IUD) with usual medical treatment in primary care

Methods

- Multicenter, randomized trial of women 25-50yo presenting to primary care for menorrhagia in UK
- Assigned to IUD vs. medical therapy
- Outcomes:
  1. Menorrhagia Multi-Attribute Scale (MMAS)- measures effects of menorrhagia on 6 domains of daily life
  3. Sexual activity- Sexual Activity Questionnaire

Results

- 84% completed questionnaires at 2 years
- Women with IUD were twice as likely to still be receiving assigned treatment at 2 years
- Discontinuation
  - IUD- 36%, lack of effectiveness, prolonged bleeding
  - Medical management- 62%, lack of effectiveness
  - Of women who d/c’d medical management, half of these changed to IUD

Results

- Both methods showed statistically significant differences in menorrhagia scores from baseline at all timepoints
- IUD group scores were significantly better across all 6 domains, all timepoints
- Subgroup analysis: women with BMI >25 showed greater benefit in scores with IUD than BMI <25
- QOL: greater benefit with IUD in all domains of SF-36 except mental health
- No difference in Euro-QOL, sexual function, or surgical intervention at 2 years

Conclusions

- Both IUD and medical management are effective for menorrhagia and improve QOL related to menorrhagia
- Scores were statistically better for IUD group
- IUD appeared more beneficial in women with BMI >25

Strengths and Limitations

- Large randomized study, good follow up rate at 2 years with robust statistics
- Primary outcomes were clinically relevant
- Low use of hormones for initial medical management (25%) which may not reflect our practice in US
- Availability of IUD as first line option for menorrhagia is questionable

Take Home Messages

- Bottom line: IUD may be a more effective first-line agent than medical therapy for menorrhagia in appropriate candidates, especially women with BMI >25

Case

- Natasha is a 23 yo female who presents to your office for vaginal discharge. You are explaining to your medical student how to collect an appropriate sample for STI testing.

What Do You Tell Him?

A. Place the probe at the cervical os, and hold in place for 15-30 seconds, being careful not to sample the vaginal discharge
B. Sample the entire vulvovaginal canal with the swab
C. Sample the entire vulvovaginal swab and then place the swab directly in the os for 15-30 seconds
Testing for Chlamydia and Gonorrhea

- Several studies have shown that self-collected vulvovaginal swabs are as sensitive (if not better?) as urethral or endocervical swabs for detection of chlamydia; sensitivity for gonorrhea is unclear.
- Current practice in the United States remains endocervical sampling for detection of STIs.
- With change in pap guidelines, we are performing less routine well-woman exams.
- Having to perform a gyno exam is a barrier to appropriate screening for STIs.

**Methods**

- Women ≥16 yo were recruited from Centre for Sexual Health at Leeds, UK.

Self-taken vulvovaginal swab

Exam: Endocervical culture, urethral culture, endocervical swab

Samples analyzed for Chlamydia and Gonorrhea

Aptima Combo 2 assay, nucleic acid amplification test (NAAT), “gold standard” for testing.

-all positive/equivocal tests were confirmed using standard guidelines.

**Results**

- 3973 women recruited by 42 separate physicians, mean age 25, mostly white.
- Prevalence:
  - Chlamydia: 10.3%
  - Gonorrhea: 2.5%
  - Co-infection: 1.4%

**Conclusions**

- Vulvovaginal testing (NAAT) is superior to endocervical testing for detection of chlamydia, regardless of symptoms.
- Vulvovaginal and endocervical samples are equal and superior to culture in detecting gonorrhea.
- Endocervical samples may miss asymptomatic urethral gonorrhea infections.
Take Home Messages

• Standard of care may be shifting away from endocervical sample collection, especially with better testing technology (NAATs)
• Consider offering self-vulvovaginal swabs for STI screening in women who otherwise would not need pelvic exam (i.e. pap is not due)

Case

Natasha’s vulvovaginal swab collected by your astute medical student during her exam returns positive for gonorrhea. Chlamydia was negative. You failed to treat her empirically at her office visit. What is the treatment of choice that you would recommend?

The News

• Since 2007, cephalosporins are the only antibiotics recommended for gonorrhea treatment
• Increased resistance to cefixime has been documented worldwide
• Neisseria gonorrhoeae Treatment Failure and Susceptability to Cefixime in Toronto, CA – Allen et al, JAMA 2013; 309(2): 163-170
• Aim: Assess risk of treatment failure of N gonorrhoeae infections associated with cefixime use

Summary

• Results: of 291 culture + isolates, treatment failure rate for oral cefixime was 6.8% (133/291, 46%)
• Most of these (7/9) were associated with increased minimum inhibitory concentrations (MICs) to cefixime on initial culture
• Of the 158 that did not return, 19.6% has increased MICs and considered high risk for failure

Gonorrhea Treatment: CDC Update August 2012

• First-line therapy:
  – Ceftriaxone 250mg IM x1 PLUS azithromycin 1gm x1 OR doxycycline 100mg BID x 7days
• Second-line:
  – Cefixime 400mg orally x1 PLUS azithromycin 1gm x1 OR doxycycline 100mg BID x 7days
  – Azithromycin 2gm orally x1

Gonorrhea Treatment Follow-Up

• All patients that do not complete first-line therapy need a test-of-cure in ONE WEEK
  – Consider NAAT swab and culture if still symptomatic
• All patients that test positive should re-screened in 3 months (high re-infection rate)

CDC gonorrhea treatment guidelines Aug 2012
Screening for Intimate Partner Violence

- Approximately 1-5 million women experience IPV annually in the United States
- IPV can result in injuries, death, STIs, unintended pregnancies and mental health issues
- In 2004, the USPSTF indicated that evidence was insufficient to support screening women for IPV

The News

- Effect of Screening for Partner Violence on Women’s Quality of Life, A Randomized Controlled Trial – Klevens et al. JAMA 2012; 308(7): 681-689.
- Aim: To assess the effect of a computerized IPV screening program and provision of IPV resource list on the quality of life of women seeking care in primary care clinics

Methods

Group 1 N=909
- Computerized Screen + IPV Resource List
  - 1 positive answer → video + IPV Resource List
  - negative answers → General Resource List

Group 2 N=893
- No computerized screening + IPV Resource List
  + General Resource List

Group 3-Control Group N=898
- No computerized screening
- No IPV Resource List
  + General Resource List

Outcomes assessed by phone interview at 1 year

Results

- 2708 women randomized, 87% follow-up
- Average age 39, 55% African American women
- ~15% reported IPV in the year before the study (no difference among groups)

Outcomes:
- QOL (SF-12)
- Days lost from work/household duties
- Use of health services
- Use of IPV resources
- Recurrence of IPV

No statistical differences among groups

Conclusions

- A computerized screening tool and provision of an IPV resource did not effect outcomes related to QOL
- Lack of efficacy may be related to brevity of intervention or 1-time occurrence
- However, IPV remains an important WH issue....

January 2013: USPSTF Updated Recommendations for IPV Screening

- "...Recommends that clinicians screen women of childbearing age for IPV ... and provide/refer women who screen positive to intervention services"
- Grade B recommendation
- Based on:
  - High prevalence: 31% of women some form of IPV (underreported)
  - Good tools: HITS, OAS/OVAT, STaT, HARK, WAST, CTQ-SF
  - Little harm
  - Decent interventions: counseling, safety plans
  - No comment on interval
Menopause and Beyond

Rachel Bonnema, MD, MS
University of Nebraska Medical Center

Case

• Marion is a 52yo non-smoker and her only medical problem is hypertension, which is well-controlled with hydrochlorothiazide. She has intolerable hot flashes and is coming to you hoping you can help her. Her mother had a heart attack at the age of 65, and Marion is worried about having one herself.

Hormone Replacement ... Timing Theory

• Women randomized to combined E/P in the Women’s Health Initiative had an increased risk for coronary heart disease and stroke
• Re-analysis of the data according to age and time since menopause suggested that younger women in early menopause might actually benefit from treatment with E/P HRT

The News

• Effect of Hormone Replacement Therapy on Cardiovascular Events in Recently Postmenopausal Women: A Randomized Trial
• Aim: To assess the effect of hormone replacement therapy on cardiovascular outcomes in early postmenopausal women

Methods

• Analysis of data from the Danish Osteoporosis Prevention Study
  – 1006 healthy recently menopausal women aged 45-58
• Open-label randomization to triphasic estradiol/norethisterone or placebo (hysterectomy: treatment with estradiol alone) for 10 years
• Outcomes:
  1) Composite outcome of death or admission for myocardial infarction or heart failure
  2) Individual components of primary endpoint, admission for stroke

Results

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Hormone Therapy (n = 500)</th>
<th>No Therapy (n = 500)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50.0</td>
<td>49.5</td>
</tr>
<tr>
<td>BMI</td>
<td>25.2</td>
<td>25.3</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>244mg/dl</td>
<td>242mg/dl</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>148mg/dl</td>
<td>148mg/dl</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>130 mm Hg</td>
<td>129 mm Hg</td>
</tr>
<tr>
<td>Years since menopause</td>
<td>0.61</td>
<td>0.58</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>84mg/dl</td>
<td>84mg/dl</td>
</tr>
</tbody>
</table>

WHI: mean age 63
WHI: 13% with increased lipids
WHI: 36% with HTN
WHI: 4% with DM
Primary endpoint and mortality for hormone replacement therapy

<table>
<thead>
<tr>
<th>Mortality, heart failure, or myocardial infarction</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥50</td>
<td>0.63 (0.29 to 1.36)</td>
</tr>
<tr>
<td>Age &lt;50</td>
<td>0.35 (0.13 to 0.89)</td>
</tr>
<tr>
<td>Had a hysterectomy</td>
<td>0.32 (0.10 to 1.00)</td>
</tr>
<tr>
<td>Had an intact uterus</td>
<td>0.37 (0.28 to 1.16)</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.57 (0.30 to 0.98)</td>
</tr>
<tr>
<td>Age ≥50</td>
<td>0.73 (0.31 to 1.68)</td>
</tr>
<tr>
<td>Age &lt;50</td>
<td>0.43 (0.16 to 1.14)</td>
</tr>
<tr>
<td>Had a hysterectomy</td>
<td>0.29 (0.08 to 1.06)</td>
</tr>
<tr>
<td>Had an intact uterus</td>
<td>0.73 (0.36 to 1.59)</td>
</tr>
</tbody>
</table>

Risk associated with HRT

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep vein thrombosis</td>
<td>2.91 (0.18 to 22.16)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.77 (0.35 to 1.70)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>0.59 (0.37 to 1.47)</td>
</tr>
<tr>
<td>Age ≥50</td>
<td>0.94 (0.53 to 1.68)</td>
</tr>
<tr>
<td>Age &lt;50</td>
<td>0.74 (0.25 to 2.11)</td>
</tr>
<tr>
<td>Had a hysterectomy</td>
<td>0.53 (0.19 to 1.48)</td>
</tr>
<tr>
<td>Had an intact uterus</td>
<td>0.60 (0.21 to 1.63)</td>
</tr>
<tr>
<td>Mortality or breast cancer</td>
<td>0.44 (0.16 to 1.17)</td>
</tr>
<tr>
<td>Age ≥50</td>
<td>0.77 (0.35 to 1.77)</td>
</tr>
<tr>
<td>Age &lt;50</td>
<td>0.36 (0.17 to 0.79)</td>
</tr>
<tr>
<td>Had a hysterectomy</td>
<td>0.53 (0.18 to 1.59)</td>
</tr>
<tr>
<td>Had an intact uterus</td>
<td>0.64 (0.25 to 1.63)</td>
</tr>
</tbody>
</table>

Conclusions

- Young, healthy, recently menopausal women who received HRT for 10 years for the primary prevention of osteoporotic fractures experienced a decreased risk for death or admission for myocardial infarction or heart failure
- There was no associated increase in stroke, breast cancer, DVT, or PE

Take Home Messages

- The findings from this study substantiate the “timing theory” but...
  - Different type and dose of estrogen used
  - Underpowered to determine effect of Estrogen monotherapy
- Minimal risk associated with therapy but...
  - Likely underpowered to detect differences in DVT/PE, CVA, and possibly breast CA
- Overall: reassured about using HRT in symptomatic healthy menopausal women, but would not prescribe for primary prevention

Case

Marion starts using a combined estrogen + progestin patch and experiences tremendous relief in her symptoms. However, she returns to your office six months later and states that she now wants to discontinue her HRT, because her sister was just diagnosed with breast cancer.

She has done some research about alternative treatments for menopause including paced respiration and wants to know your opinion on this for treatment of hot flashes.

You tell Marion:

A. The only effective treatment for hot flashes is hormonal therapy.
B. Paced respiration is a tried and true remedy for hot flashes with good clinical evidence.
C. Paced respiration is a good option for her, she should take fast, shallow breaths at the start of the hot flash.
D. Paced respiration aims for 6-8 breaths/minute.
Non-hormonal Treatments for Menopause

- Vasomotor symptoms are the cardinal symptoms of menopause
- Many women, including breast cancer survivors are unable to take certain pharmacologic therapies
- Paced respiration has been internationally recommended
  - Based on insufficient empirical evidence

The News

- Paced Respiration for Vasomotor and Other Menopausal Symptoms: A Randomized, Controlled Trial
  - Aim: To evaluate efficacy of a paced respiration intervention against attention control and usual care for menopausal symptoms

Methods

- Peri/post-menopausal community women and breast cancer clinics
  - ≥2 hot flashes per 24hr day of ≥moderate severity
- 16wk, 3 group, partially-blinded, RCT
  - Assessments at baseline, 8wk, 16wk
  - Intervention: 2-wk assessment of learning/performance done by non-blinded staff (not involved in data collection)
  1. Paced respiration—practice twice daily for 15 mins and at onset of hot flash
  2. Fast, shallow breathing
  3. Usual care

Results

- 218 women, 96 breast cancer survivors

<table>
<thead>
<tr>
<th>Paced Respiration n=88</th>
<th>Breathing control n=86</th>
<th>Usual Care n=44</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flash frequency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>7.02 (4.32)</td>
<td>6.43 (3.96)</td>
<td>7.31 (4.04)</td>
</tr>
<tr>
<td>8 weeks</td>
<td>4.28 (4.04)</td>
<td>4.66 (4.40)</td>
<td>5.12 (3.35)</td>
</tr>
<tr>
<td>16 weeks</td>
<td>3.48 (3.45)</td>
<td>3.95 (4.19)</td>
<td>4.76 (3.54)</td>
</tr>
<tr>
<td>% achieving 50% reduction in hot flashes (sustained at 16 wks)</td>
<td>38%</td>
<td>29%</td>
<td>22%</td>
</tr>
</tbody>
</table>

Conclusions

- Paced respiration is unlikely to provide clinical benefit for vasomotor symptoms
  - Some minor benefits seen for sleep, not likely to be clinically meaningful
- Participants were able to demonstrate appropriate learning of paced respiration
Take Home Messages

- Paced respiration is not more efficacious than usual care
- Clinicians should be prepared to discuss the relative lack of empirical support for this therapy

Case

- Florence is a 68yo woman in for follow up of hyperlipidemia and thyroid disease. She admits during ROS she has to wear a pad daily and has difficulty “making it to the bathroom in time”. She has tried minimizing her fluid intake and scheduling bathroom breaks but admits this has quite a negative impact on her life.

Case

- What do you advise as her next steps?
  A. Referral for pessary
  B. Begin trospium, there is clear benefit for this medication over any other
  C. Begin a medication for urge incontinence, whatever is first tier on her insurance plan
  D. Refer for pelvic floor muscle training

Background

- Older women: urinary frequency and urgency with or without urge incontinence
- Initial treatments: lifestyle changes, bladder retraining, pelvic floor strengthening
- Several medications have been approved
  - Medications have high rates of anti-cholinergic side effects
- Previous reviews have not emphasized continence or quality of life (QOL) as outcome

The News

- Benefits and Harms of Pharmacologic Treatment for Urinary Incontinence in Women: A Systematic Review
- Aim: To conduct a systematic literature review of drugs for urgency urinary incontinence in women.

Methods

- Objectives:
  1. Analyze efficacy, safety and comparative effectiveness of drugs for patient centered outcomes
  2. Analyze long-term adherence to drug treatment
  3. Analyze which characteristics of women can modify treatment effects

Methods

• Defined clinically important improvement in UI as ≥50% reduction in UI frequency
  – Calculated pooled RR and AR difference for efficacy outcomes
• QOL according to minimal clinically important differences in validated scales
• Performed meta-analysis of direct results from head-to-head comparisons for comparative effectiveness

Results

• Drugs were more effective, but with low magnitude of effect
  • Fewer than 200 cases/1000 treated were attributable to drugs
  • Absolute risk difference in continence was <20% for all drugs
  • 21 head-to-head RCTs comparing drugs suggest similar effectiveness but different safety

Conclusions

• Strong evidence that rates of continence and clinically important improvement in UI were greater with drugs than placebo
  – All drugs were better than placebo and had similar effectiveness
  – Benefits from drugs are small
• Drugs caused treatment discontinuation due to side effects

Key Article

• Urinary Incontinence in Young Nulligravid Women: A Cross-sectional Analysis
• 1002 nulligravid women, mean age 22.5yrs
• Rate of any UI: 12.6% (10.5-14.7)
  – Ever sexually active, no COC use: 21.5% (16.7-27.3)
  – Never sexually active, no COC use: 10.1% (7.0-14.4)
• UI associated with poorer indexes of health-related QOL
Take Home Messages

• Ask about UI—in all women
• UI is associated with lower QOL
• Medications have small magnitude of benefit, side effects causing discontinuation of treatment
• All drugs for urgency UI have similar effectiveness

Cancer Screening and Risk Factors

Judith Walsh, MD, MPH
University of California, San Francisco

The Mammography Controversy Continues

Case

• Stella Skeptic is a 58 year old woman who doesn’t believe in “conventional medicine.” She has previously declined all your preventive recommendations, including screening mammography and CRC screening. She comes in today wanting to know what you think about “that new study” that shows that mammography really doesn’t work that well after all.”

Screening Mammography and Mortality

• Screening should lead to diagnosis of earlier stage cancers
• Early treatment of these detected cancers should lead to more benefit then treatment given at time of clinical presentation
• Effective screening programs should lead to a reduction in the diagnosis of late stage cancers

The News

• Effect of three decades of screening mammography on breast cancer incidence
  – Bleyer and Welch, NEJM 2012
• Aim: To quantify the expected increase in the incidence of early stage breast cancer and to determine the extent to which this has led to a corresponding decrease in the incidence of late stage cancer
Methods

• SEER data (1976 to 2008) to evaluate trends in incidence of early stage breast cancer (DCIS and localized disease) and late stage breast cancer (regional and distant disease) among women aged 40 and over
• NHIS data on proportion of women undergoing screening mammography
• Estimates adjusted for transient increase associated with hormone therapy use from 1990-2005

Results

• Screening mammography associated with a doubling in the number of cases of early stage breast cancer found annually
  – 112 to 234 cases/100,000 women
• Rate of presentation with late stage breast cancer has decreased by 8%
  – 102 to 94 cases per 100,000 women
• Assuming constant underlying disease burden, 8 of the additional 122 cancers detected expected to progress to advanced disease

Results: Over-diagnosis

• Over-diagnosis: tumors detected by screening that would never have led to clinical symptoms
• Adjusting for trends in breast cancer incidence, estimate for over-diagnosis
  – In 2008 over 70,000 women (31% of all breast cancers diagnosed)

Take Home Message

• Screening mammography has led to a substantial increase in the diagnosis of early stage breast cancers, with only a small reduction in the rate of late stage breast cancer
• The reduction in mortality from screening appears to be smaller and the risk of over-diagnosis higher, than previously believed.

Screening Women in Their Forties

• USPSTF recommends individualized, informed decision making based on a woman’s values about benefits and harms
• Women with a two fold risk of breast cancer who start biennial screening in their forties have similar benefits and harms as average risk women who start screening at age 50
  • CISNET Microsimulation Models (Van Ravesteyn, 2012)
• Identifying women with at least a two fold increased breast cancer risk could be useful in decision making about mammography initiation before age 50

Case

• Suzie Screening has just turned 40. Her gynecologist gave her a referral for a mammogram but her best friend said that her doctor told her not to have one. Suzie’s head is spinning because every day she hears something different and she wants to know what you, her primary care physician, think. What do you tell her?
What do you recommend to Suzie?

- Yes, of course. All women should have their first mammogram at age 40.
- No, wait until you are 50.
- Let’s talk about it (even though you are already 20 minutes behind)
- We can talk about this next time you come in (maybe the guidelines will be more clear then)
- I don’t know… what do you want to do?

The News

- Risk factors for breast cancer for women aged 40 to 49 years: a systematic review and meta-analysis
- Aim: To determine which factors increase risk for breast cancer in women aged 40 to 49 and the magnitude of risk for each factor

Methods: Systematic Review

- Main outcome:
  - Incidence of invasive breast cancer at age 40-49
  - Combined outcome: invasive and non-invasive breast cancer if only available outcome
- Risk factors: Race/ethnicity, BMI, physical activity, alcohol use, smoking, family history of breast cancer, breast density, prior breast procedures, reproductive factors
- Relative risks or odds ratios used as effect measures
  - Only studies measuring at least one confounder were included
- Data from Breast Cancer Surveillance Consortium (BCSC) to supplement systematic review
  - 5 mammography registries and two affiliate sites
  - Some risk factors not reported in published studies

Results

- Personal Risk Factors: No association race, ethnicity, BMI, physical activity, alcohol or smoking
- Family history
  - RR 2.14 (CI 1.92-2.38) one first degree relative
  - RR 3.84 (2.37-6.22) with 2 relatives
  - RR 12.05 (1.70-85.16) for ≥3 relatives
  - Risk higher if relative diagnosed at younger age
- Breast density (BI-RADS category 2 as reference)
  - RR 1.62 (CI 1.51-1.75) for BI-RADS 3
  - RR 2.04 (CI 1.84-2.26) for BI-RADS 4

Results: Reproductive Factors

- Menarche at age 15 or older associated with reduced risk compared with reference (13 years)
  - RR 0.87 (CI 0.79-0.97)
- Reduced risk for women with 3 or more births (reference nulliparous)
  - RR 0.73 (CI 0.61-0.87)
- Breast feeding associated with reduced risk
  - RR 0.87 (CI 0.77-0.98)
- Oral contraceptive use
  - No association in meta-analysis
    - BCSC data showed higher risk for current OC use compared with former or never use
      - RR 1.38 (CI 1.13-1.69)

Results: Magnitude of Risk

- Greater than two fold increased risk
  - First degree relative with breast cancer
  - Extremely dense breasts on mammography
- 1.5 to 2.0 times increased risk
  - Prior benign breast biopsy result
  - Second degree relative with breast cancer
  - Heterogeneously dense breast tissue
- 1.0 to 1.5 times increased risk
  - Current use of OCPs
  - Nulliparity
  - First birth at age 30 or over
  - Results differed by data sources (inconsistency)
Results: Lower than Average Risk

- BMI of 25 kg/m² or higher
- Low breast density
- Age 15 or older at menarche
- Birth of 3 or more children
- Breastfeeding
- Perimenopausal or postmenopausal
- Use of menopausal estrogen only hormone therapy

Take Home Message

- High breast density and having a first degree relative with breast cancer are factors that could be useful in developing a personalized approach to breast cancer screening.

Key Article

- Institute of Medicine recently published a report on environmental causes of breast cancer and radiation from medical imaging
- Two environmental factors most strongly associated with breast cancer are exposure to ionizing radiation and to combined postmenopausal hormone therapy
- Some lifestyle factors may modestly limit breast cancer risk:
  - Limiting alcohol use, maintaining a healthy body weight and reducing active smoking

IOM Report Conclusions

- Current evidence based options for breast cancer reduction are limited
- Many risk factors are not modifiable
- Avoiding and reducing exposure to medical radiation is an evidence based strategy that could reduce breast cancer risk:
  - Radiation doses from CT are particularly high
  - Reducing unnecessary exposures

Cervical Cancer Screening

New Recommendations

<table>
<thead>
<tr>
<th>USPSTF 2012</th>
<th>ACG/American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology Joint Guidelines 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pap smear every 3 years in women aged 21-65</td>
<td>Pap every 3 years in women aged 21-29</td>
</tr>
<tr>
<td>For women aged 30-65 who want to lengthen the screening interval, screen with a combination of cervical cytology and HPV testing every 5 years</td>
<td>For women aged 30-65 Pap plus HPV testing is the preferred method</td>
</tr>
<tr>
<td>Discontinue in women over the age of 65 in whom smear has been consistently normal</td>
<td>Discontinue in women over the age of 65 in whom smear has been consistently normal</td>
</tr>
<tr>
<td>No HPV screening in women younger than 30</td>
<td>No HPV testing in women less than age 30</td>
</tr>
<tr>
<td>No screening in women who have had a hysterectomy</td>
<td>No screening in women who have had a hysterectomy and have no history of cervical cancer or pre-cancer</td>
</tr>
</tbody>
</table>
**Bone Health**

Dietary vs Supplemental Calcium

**Case**

- Bonnie Bony is a 71 year old woman with hypertension and hyperlipidemia. She has a family history of osteoporosis and her BMD t score last year was -2.4. She is here for her annual examination and as you review her medications with her she tells you that she has stopped her calcium because she has heard that it "might be bad for the heart." What do you advise her?

**What do you advise Bonnie?**

- You need to restart it right away- you are at high risk for a fracture.
- Good idea, stay off of it
- As long as you drink plenty of milk, you should be fine.

**Calcium and Cardiovascular Disease**

- Calcium supplements are widely recommended for bone health
- Previous studies have shown that calcium is necessary but not sufficient for reducing osteoporosis risk
- Recent studies have suggested an increase in cardiovascular events with supplemental calcium, but the role of dietary calcium intake has been less clear

**The News**

- Associations of dietary calcium intake and calcium supplementation with myocardial infarction and stroke risk and overall cardiovascular mortality in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition study (EPIC-Heidelberg)
  - Li et al, Heart, 2012
- Aim: To examine the associations of dietary calcium intake and calcium supplementation with MI and stroke risk and overall CVD mortality

**Methods**

- 25,540 residents of Heidelberg aged 35-64 recruited in 1994-8
  - Excluded those with MI, stroke or TIA at baseline and those with outlying nutritional intakes
  - 23,980 included in analysis
- Validated food frequency questionnaire consumption of 148 items in preceding 12 months
- Self reported supplement use
- Self reported cardiovascular events were verified
Results

• Higher dietary calcium intake was associated with younger age, higher education, higher level of physical activity, less likelihood of being overweight
• Dietary calcium intake associated with Vitamin D intake and likelihood of taking calcium supplements
• Average duration of follow-up 11 years

Results: Dietary Calcium

• Total of 354 MIs, 260 strokes and 267 CVD deaths
• Third quartile of dietary calcium and dairy calcium intake had a decreased risk of MI compared with first quartile
  – HR 0.69 (95% C.I. 0.50-0.94) dietary
  – HR 0.68 (95% C.I. 0.50-0.93) dairy
  – Trend was not significant
• Gender subgroup analyses
  – Men: HR 0.80 (95% C.I.: 0.56-1.14)
  – Women: HR 0.43 (95% C.I.: 0.22-0.82)

Results: Calcium Supplements

• Calcium supplement users had an increased risk of MI compared with nonusers
  – HR 1.86 (95% C.I. 1.17 -2.96)
  – HR 2.39 (95% C.I. 1.12-5.12) for calcium only
• No association between calcium supplements and other CV outcomes

Conclusions

• Calcium supplements were associated with a small increased risk of MI, but were not associated with other cardiovascular outcomes
• Dietary calcium intake was not associated with cardiovascular benefits

Take Home Message

• Encouraging adequate dietary calcium intake should be an important goal
• Consider judicious use of calcium supplements in individuals at high risk for CVD.

USPSTF Recommendations

February, 2013

• Evidence is insufficient to assess balance of benefits and harms
  – 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
Questions?