Women in Midlife: Menopause & Osteoporosis

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UCSF CME Conference
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Outline for Menopause

• Definitions
• Summary of the Evidence
• Current Guidelines
• Management of Menopausal Symptoms

STRAW Stages of the Menopausal Transition-NAMS, 2012
Symptoms of Menopause

Most Common

• Hot flashes
• Night sweats
• Insomnia

Others

• Poor concentration
• Vaginal dryness & dyspareunia
• Decreased libido
• Mood changes
• Anxiety
• Weight gain
• Bloating
• Heart palpitations
• Breast tenderness
• Incontinence

North American Menopause Society
2010 Position Statement: TREATMENT

<table>
<thead>
<tr>
<th></th>
<th>FDA-Approved for this indication</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasomotor Symptoms</td>
<td>Yes</td>
<td>**Primary indication for HT</td>
</tr>
<tr>
<td>Vulvar/Vaginal Atrophy</td>
<td>Yes</td>
<td>Local treatment recommended</td>
</tr>
<tr>
<td>Early Menopause</td>
<td>Yes</td>
<td>Until age 52 years</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>Yes</td>
<td>Not approved for other sexual problems (libido)</td>
</tr>
<tr>
<td>Bone Health</td>
<td>Yes-Preservation</td>
<td>Extended use an option when alternative treatment not available</td>
</tr>
</tbody>
</table>

Guidelines for HT Management

American College of Obstetrics & Gynecology 2002

- Counsel women about risks and benefits
- Include risk reduction: diet, exercise, weight management, smoking cessation, and alcohol reduction
- Lowest dose, shortest duration

North American Menopause Society 2008 & 2010

- Counsel women about risks and benefits
- Treat women with moderate to severe vasomotor sx or to prevent risk of fracture in some high-risk women
- Lowest effective dose that meets treatment goal
- Not longer than 3-5 years
- Should not be initiated in women ≥ 60 years

US Preventative Health Services Task Force 2005

- Against routine use of HRT for prevention of chronic disorders in postmenopausal women

Women’s Health Initiative: Risks and Benefits of Hormone Therapy

<table>
<thead>
<tr>
<th>Medical Condition</th>
<th>Relative Risk Compared to Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip Fracture</td>
<td>0.61 *</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>0.77</td>
</tr>
<tr>
<td>CHD</td>
<td>0.91</td>
</tr>
<tr>
<td>Total Mortality</td>
<td>1.04</td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td>1.08</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.39 *</td>
</tr>
</tbody>
</table>

* p<0.05

Source: Adapted from WHI Steering Committee 2004
Women’s Health Initiative: Risks of Hormone Therapy

<table>
<thead>
<tr>
<th>Risks*</th>
<th>Absolute Risk per 10,000 person years</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>May reduce risk of MI if started in 1st 10 years of menopause, ↑ risk thereafter</td>
<td>7</td>
</tr>
<tr>
<td>Stroke</td>
<td>↑ risk Starts at onset of medication, return to baseline after d/c medication</td>
<td>8</td>
</tr>
<tr>
<td>VTE/PE</td>
<td>↑ risk Starts at onset of medication, return to baseline after d/c medication</td>
<td>18</td>
</tr>
<tr>
<td>Breast CA</td>
<td>↑ risk, starts after &gt;3-5 with HT</td>
<td>8</td>
</tr>
</tbody>
</table>

*at >5 years follow-up  † per 10,000 person years

Women’s Health Initiative: Benefits of Hormone Therapy

<table>
<thead>
<tr>
<th>Reduced Risks*</th>
<th>Absolute Risk Reduction per 10,000 women/year</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal CA</td>
<td>EPT arm only, No effect with ET</td>
<td>6</td>
</tr>
<tr>
<td>Osteoporotic Fractures</td>
<td>Hip, spine and combined sites ↓ No FDA-approval for treatment, only prevention</td>
<td>5</td>
</tr>
<tr>
<td>Incidence of Diabetes</td>
<td>EPT/ET arms Reduces onset Reduces medication requirements</td>
<td>15/14</td>
</tr>
<tr>
<td>Demensia</td>
<td>Mixed results from WHI</td>
<td>↓†</td>
</tr>
</tbody>
</table>

HT and Primary Prevention for Cardiovascular Disease

• Significant reduction in CHD risk among women 50-59 years in WHI HT
• Significant reduction in CHD risk by age group
  - 50 to 59 years HR=0.93
  - 60 to 69 years HR=0.98
  - 70 to 79 years HR=1.26 (p=0.05)
• Significant excess in CHD risk by years since menopause
  - <10 years HR=0.76
  - 10 to 19 years HR=1.10
  - >20 years HR=1.28 (p=<0.02)

Contraindications to Use of Systemic HT

• Risk stratify women 50 to 59 years of age
  - History of DVT/PE
  - History of MI/CVA
  - History of Breast Cancer
  - History of active liver disease
  - Triglycerides >500 mg/dL
• Less clear
  - Early family history of DVT/CVD/Breast Cancer
  - Men versus women with Breast Cancer
  - First degree relatives with Breast Cancer

Differences in Cardiovascular Risk by Type of Estrogen

- Decreased risk for atherosclerosis as measured by carotid artery intima-media thickness with 17-beta-estradiol 1mg/day
  - Estrogen in Prevention of Atherosclerosis Trial (EPAT)
    - Karim, 2008
- Reduced risk of MI and CVA with esterified estrogens v CCE
  - Angerer, 2001

Little Difference in Cardiovascular Risk by Route of Estrogen

- Likely similar incidence of cardiovascular risk
  - Oral HT
    - First-pass effect yields more reduction in:
      - Lower LDL
      - Lower lipo-protein a
      - Less insulin resistance
      - Higher HDL
  - Transdermal HT
    - Lack of first-pass effect yields
      - Higher triglycerides
      - More activated coagulation pathways

HT and Secondary Prevention of Cardiovascular Disease

- No improvement in CHD or all cause mortality
- No difference in type of estrogen
- No difference in age
- Do not use HRT for secondary prevention of CHD

HT and Breast Cancer Risk

- ↑ risk of breast cancer with prolonged exposure to HT
- ↑ risk at <3-5 years use not significant
- Risk goes down after cessation
- Initiation of combined therapy early after menopause may confer MORE risk
- Additional risk with use of progesterone
- Additional risk with ≥ 2 alcoholic drinks/day
Cessation of Hormone Therapy

• Evidence for taper
  – Oral Estrogen or Combined Regimens
    • Quick Taper over 6 weeks
    • Long Taper over 6 months to 1 year
  – Transdermal Estrogen
    • Using decreased doses in each patch over time

Treatment Options for Vasomotor Symptoms Beyond HT

Combined Oral Contraceptives

• Hot flashes start in early menopausal transition
• Perimenopausal women are still fertile
• If considering OCP
  – Screen for CVD first
    • If High risk, don’t give E+P
  – If high risk, alternatives for indication of bleeding
    • Progestin-only pill
    • Mirena IUD
    • Depo-provera

Anti-Depressants for Vasomotor Symptoms

• Selective Serotonin Reuptake Inhibitors
  – Fluoxetine
    • 50% versus 20% ↓ hot flashes
  – Escitalopram
    • 47% versus 33% ↓ hot flashes
• Serotonin/Norepinephrine Reuptake Inhibitors
  – Venlafaxine 75mg
    • 61% versus 20% ↓ hot flashes
    • Small study for 4 weeks, 12 week study with no benefit
• Less clear benefit
  – Citalopram & Sertraline
Other Medications for Vasomotor Symptoms

• Clonidine
  – Used for menopausal flushing
  – PO 0.1-0.4 mg/day divided BID to TID
  – Transdermal 0.1 mg/day applied weekly
    • Titratable
    • Not shown efficacy greater than placebo
• Gabapentin
  – PO 900 mg/day divided TID

Testosterone for Vasomotor Symptoms

• Treatment for vasomotor symptoms
  – Estrogen + Testosterone* in combination
  – Variable effects in a few studies
• Treatment for decreased libido
  – Some evidence of benefits to sexual function, libido, and arousal
  – Other benefits
    • ↑ bone composition, muscle strength, QOL
  – Other risks
    • ↑ breast cancer risk in Nurses Health Study
    • Side effects: acne, virilization, ↓ HDL

Complementary & Alterative Medicine Effect on Hot Flashes

Some Effect Possible
• Black cohosh
• Soy isoflavones
  – Estrogenic effects inconclusive
• Bio-identical hormones
  – Estrogenic effects
  – Natural but not physiologic
No Proven Effect
• Vitamin E (800 IU/day)
• Phyto-estrogens
• Dong Quai
• Ginsing
• Evening Primrose Oil
• Wild yam

Key Points

• Use HRT in the lowest effective dose for the shortest amount of time for menopausal symptoms
• Evidence does not support routine use of HRT for prevention of chronic conditions in post-menopausal women
• Few indications for HT in women > 60 years of age
• Women must be risk-stratified on an individual basis & be made aware of the risks and benefits of HRT use

Outline for Osteoporosis

• Epidemiology
• Guidelines for Screening
• Screening Tools and Pitfalls
• Treatment Options
• Vitamin Supplements & Other Prevention

Impact of Fractures

• Fractures caused by osteoporosis affect 1 in 2 women and 1 in 5 men over 50 years of age
• Results in permanent disability in over 30% of those with fracture
• After hip fracture, nearly 20% will die within 1 year
  — Prevalence of death is twice as high in men
• Over 50% of survivors will not return to independent living
• Direct spending is about 18 billion dollars annually
**Guidelines for Screening for Osteoporosis in Women**

<table>
<thead>
<tr>
<th>Organization</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Osteoporosis Foundation 2008</td>
<td>- Screen all women &gt; 65 years regardless of risk</td>
</tr>
<tr>
<td></td>
<td>- Screen all men ≥ 70 years regardless of risk</td>
</tr>
<tr>
<td></td>
<td>- Screen postmenopausal women &amp; men 50-69 years with significant risk factors</td>
</tr>
<tr>
<td>North American Menopause Association 2010</td>
<td>- Screen all women at 65 years</td>
</tr>
<tr>
<td></td>
<td>- Screen women at 50 years of age if ↑ risk</td>
</tr>
<tr>
<td></td>
<td>- Screen postmenopausal women age with medical causes of bone loss</td>
</tr>
<tr>
<td></td>
<td>- Screen postmenopausal women with a fragility fracture</td>
</tr>
<tr>
<td>USPSTF 2001</td>
<td>- Screen all women ≥ 65 years</td>
</tr>
<tr>
<td></td>
<td>- Screen women at 60 years if ↑ risk</td>
</tr>
<tr>
<td></td>
<td>- Insufficient evidence to support screening younger women</td>
</tr>
</tbody>
</table>

**Are we following the guidelines?**

Study Group: 615 women who were screened with DXA between 2007 and 2009

**Question 1:** Should these women have been screened?
- 41% did not meet criteria for screening

**Question 2:** Of those who met criteria for treatment, were they treated?
- With an indication, 35% were treated
- With no indication, 18% were treated


**When to Screen for Osteoporosis**

- All women 65 years and older
- All Men 70 years and older
- Women <65 and men <70 years with increased risk
- Any fragility fracture
  - DO NOT Screen, move on to TREATMENT

**Major Risk Factors for Fracture**

- Low-impact fracture as an adult
- History of fractured hip in a parent
- Current smoking
- Rheumatoid Arthritis
  - Use of oral corticosteroid therapy for more than 3-6 months
  - Alcohol in amounts >2 drinks per day (>3 oz/day)
- Low body weight (BMI ≤19)
- Disorders associated with secondary osteoporosis
  - Type 1 DM
  - Untreated, longstanding hyperthyroidism
  - Hypogonadism or premature menopause
  - Chronic malnutrition/malabsorption
  - Chronic liver disease
The Pitfalls of Screening with DEXA

- Sites give varying results
  - Wrist & heel less predictive of fracture
  - Less responsive to treatment
  - Cheaper
- Femoral Neck versus Total Hip
  - Hip as fracture site LIKELY more predictive
  - Both good
- One site versus composite of many sites
  - About the same cost, not better predictors as a sum
- PA versus lateral lumbar spine
  - Be careful of false positives due to DJD
- Do not use Ward’s Triangle
- Complicated comparisons over time
  - By reviewer
  - By machine

82% of fractures are not in women with osteoporosis on DEXA

World Health Organization Diagnostic Criteria

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>BMD Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>BMD within 1.0 SD of the T-score</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>BMD -1.0 to -2.5 SD below the T-score</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>BMD ≤ -2.5 SD below the T-score</td>
</tr>
<tr>
<td>Severe Osteoporosis</td>
<td>Fragility fracture PLUS BMD ≤ -2.5 SD below the T-score</td>
</tr>
</tbody>
</table>

- Z-score = mean BMD relative to age matched adults
- T-score = mean BMD relative to 30 year-old adults
When to Re-Screen for Osteoporosis

<table>
<thead>
<tr>
<th>DEXA Result</th>
<th>T-Score</th>
<th>Interval to Re-Screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Osteopenia</td>
<td>-1.0 or higher</td>
<td>15 years</td>
</tr>
<tr>
<td>Mild Osteopenia</td>
<td>-1.5 to -1.0</td>
<td>15 years</td>
</tr>
<tr>
<td>Moderate Osteopenia</td>
<td>-1.5 to -1.99</td>
<td>5 years</td>
</tr>
<tr>
<td>Severe Osteopenia</td>
<td>-2.0 to -2.49</td>
<td>1 year</td>
</tr>
</tbody>
</table>

Adapted from N Engl J Med 2012;366:225-33

When to Treat Osteoporosis

- **FRAX® Model Output:** women and men >50 years of age with 10-year risk of hip fracture >3% or any fracture >20%
- Low trauma fracture in someone ≥ 45
- History of low-impact fracture
- BMD > -2.5 SD away from T-score mean
- Loss of height > 1.5 inches regardless of BMD

Osteoporosis Prevention & Treatment with Bisphosphonates

<table>
<thead>
<tr>
<th>Medication</th>
<th>Regimen</th>
<th>Prevention</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>35 mg/week 70 mg/week 10 mg/day</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Risedronate</td>
<td>150 mg/month 35 mg/week</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>150 mg/month 2.5 mg/day 3 mg IV/q3 mo</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Zoledronic Acid*</td>
<td>5 mg IV/q12 mo 5 mg IV/q24 mo</td>
<td>√</td>
<td>√</td>
</tr>
</tbody>
</table>

Bisphosphonate Dosing Factoids

- All have equivalent efficacy for reducing vertebral and non-vertebral fractures
- Take on empty stomach with 8 oz water, then sit upright for 30 minutes
  - Risk for erosive esophagitis
- WEEKLY dosing has BEST adherence
- Ideal duration UNCLEAR: 5 -10 years?
- Renal dosing required if CLcr <30 mL/min

* 3 years MAX
Osteoporosis Prevention with Other Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Regimen</th>
<th>Prevent’n</th>
<th>Treatm’tnt</th>
<th>Frx ▼</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raloxifene*</td>
<td>60 mg/day</td>
<td>✓</td>
<td>✓</td>
<td>Vertebral</td>
</tr>
<tr>
<td>(Evista)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denosumab</td>
<td>60 mg SC q6 mo</td>
<td>✓</td>
<td></td>
<td>Vertebral</td>
</tr>
<tr>
<td>(Prolia)</td>
<td></td>
<td></td>
<td></td>
<td>Non-vert</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>200 IU IN/day</td>
<td>✓</td>
<td>✓</td>
<td>Vertebral</td>
</tr>
<tr>
<td></td>
<td>100 IU SC/day</td>
<td>✓</td>
<td>✓</td>
<td>Non-vert</td>
</tr>
<tr>
<td></td>
<td>100 IU IM/qod</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTH</td>
<td>20 mcg SC/day</td>
<td>✓</td>
<td></td>
<td>Vertebral</td>
</tr>
<tr>
<td>(Forteo)</td>
<td></td>
<td></td>
<td></td>
<td>Non-vert</td>
</tr>
</tbody>
</table>

*anti-estrogen effects on uterus and breast. ▼ VTE, CVA

Institute of Medicine
Vitamin D and Calcium

Calcium
- Adults 19-50 years 1000 mg/day
- Men >50 years of age 1000 mg/day
- Women >50 years of age 1200 mg/day
- Men >70 years of age 1200 mg/day

Vitamin D
- Adults up to age 70 years 600 IU/day
- Adults above age 70 years 800 IU/day

NOTE:
- Consider *calcium citrate* because less dependent on stomach acid for absorption (NOF, 2008)
- *Adherence* of about 80% shows best BMD (WHI)

Osteoporosis Prevention with Estrogen Preparations

- Oral Estrogens
  - Estradiol, Estriol, Estrogens, Estolate, CEE
- Oral Estrogen-Progestin Combination
  - Estradiol + Progestin or progestin
  - CEE+medroxyprogesterone

Transferm Estrogens
- Estradiol

Transferm Estrogen-Progestin Combinations
- Estradiol + levonorgestrel

Calcium and Vitamin D Associated with Risk for CHD

- WHI: Calcium and Vitamin D Supplementation Study
  - Followed 32,282 women for 7 years
  - RCT: Calcium 1000mg and Vitamin D 400 IU versus personal supplementation
    - Risk of MI
      - HR 1.14 (p=0.05)
    - Risk of CVA plus MI
      - HR 1.22 (p=0.04)
Fall Prevention

- 90% of hip fractures associated with a fall
- Review medications
  - BDZ
  - Anti-depressants
  - Pain medication
  - Anti-convulsants
  - Sedatives
    - ↓ falls by 60%

Summary

- Screen women ≥ 65 years, Men ≥ 70 years
- Risk stratify younger women
- Treat women with bisphosphonates when indicated
- Give ENOUGH vitamin supplementation
- REDUCE fall risk
References

2. North American Menopause Society
3. US Preventive Health Services Task Force