When Ovaries Retire Too Soon
Risks for CVD and Fracture

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When Ovaries Retire Too Soon

Menopause
Spontaneous
Induced

Autoimmune
- Cyclophosphamide
Cancer Rx
- Chemo
- Pelvic RT

Bilateral Oophorectomy

When Ovaries Retire Too Soon

Menopause transition
20s 30s 40s 50s 60s 70s 80s+
Reproductive
Premenopause
Postmenopause

<40 years
Early Menopause

Potential Perils of Premature or Early Menopause

Cardiovascular
- Increased: CHD, CVD mortality, Total mortality, Impaired endothelial function

Bone
- Low BMD, Early osteoporosis and fracture

Quality of Life
- Decreased general and sexual wellbeing

Psyche
- Anxiety, Depression

Early Menopause and CVD Risk
Type of Menopause (18 study meta-analysis)

Pooled RR CVD
- Postmenopausal 0.96
- Bilateral oophorectomy 2.62
- Early menopause 1.38

*Adjusted for age and smoking

Spontaneous Premature Menopause
Mortality and Cardiovascular Risk

Author Year Group Mortality All-Cause CVD Mortality CHD
Snowden 1989 Adventists ↑ GR 1.95
Jacobsen 1999 Adventists ↑ ↑
Ho 1999 Nurses' ↑
Jacobsen 2003 Norwegian ↑
Van der Schouw 1996 Netherlands ↑
Ossenwaarde 2005 Netherlands ↑
Lukkagaard 2006 Danish ↑
Li 2013 Black Women ↑

**Premature Menopause and CHD**

Nurses’ Health Study 1976-1994

- Multivariate relative risk of CHD across ages at natural menopause
- All women:
  - < 40: 1.53
  - 40-44: 1.42
  - 45-49: 1.10
  - 50-54: 1.0
- Never smokers:
  - 0.92
  - 0.98
  - 1.12
  - 1.0


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**Spontaneous Early Menopause**

Mortality and Cardiovascular Risk

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Group</th>
<th>Mortality All-Cause</th>
<th>CVD Mortality</th>
<th>CHD</th>
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<tbody>
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<td>Jacobsen</td>
<td>1997</td>
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<td>de Kleijn</td>
<td>2002</td>
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<td>Mondul</td>
<td>2005</td>
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<td>Cui</td>
<td>2006</td>
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<tr>
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<td>MESA &lt; 46</td>
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</table>

Shuster LT, Maturitas 2010;65:161-166.

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**Spontaneous Premature / Early Menopause**

Stroke Risk

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Group</th>
<th>Age at Menopause</th>
<th>Stroke Risk</th>
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<tbody>
<tr>
<td>Hu</td>
<td>1999</td>
<td>Nurses</td>
<td>&lt; 40</td>
<td>NS</td>
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<tr>
<td>Jacobsen</td>
<td>2004</td>
<td>Norwegian</td>
<td>&lt; 40</td>
<td>NS</td>
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<tr>
<td>Baba</td>
<td>2010</td>
<td>Japanese</td>
<td>&lt; 40</td>
<td>NS</td>
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<tr>
<td>Lisabeth</td>
<td>2009</td>
<td>Framingham</td>
<td>&lt; 42</td>
<td>HR 2.0</td>
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<td>Cui</td>
<td>2006</td>
<td>Japanese</td>
<td>&lt; 44</td>
<td>NS</td>
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<tr>
<td>Wellons</td>
<td>2012</td>
<td>MESA</td>
<td>&lt; 46</td>
<td>HR 2.19</td>
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**Heart Disease Risk Determines Menopausal Age (rather than the reverse)**

- Framingham Heart Study Cohort
- Correlated premenopausal CHD risks with age at menopause
- Each 1% higher premenopausal Framingham risk score was associated with a decrease in menopausal age of 1.8 years


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**Which came first: The chicken or the egg?**

**Hypothesis 1:**
- Premature or early menopause is the first step in a chain of causality leading to tissue or organ dysfunctions and lesions via hormonal mechanisms.

Shuster LT, Maturitas, 2010

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**Which came first: The chicken or the egg?**

**Hypothesis 2:**
- Premature or early menopause is the result of an accelerated aging process determined by genetic or nongenetic causes and involving all tissues and organs throughout the body, including the ovaries.

Shuster LT, Maturitas, 2010
Reproductive Aging and Premenopausal Cardiovascular Risk

- 951 participants of the Ovarian Aging Study (OVA)
- Kaiser Permanente Northern California
- Multiethnic women
- 25 to 45 years of age
- Regular menses
- Uterus and both ovaries intact


Reproductive Aging and Premenopausal Cardiovascular Risk

- Correlated measurements of:
  - Antimullerian hormone (AMH)
  - Components of metabolic syndrome
    - Triglycerides
    - HDL cholesterol
    - HOMA-IR (fasting glucose and insulin)
    - Waist circumference
    - Hypertensive status


Reproductive Aging and Premenopausal Cardiovascular Risk

- When all analyses were repeated with additional adjustment for BMI, associations between AMH and total cardiometabolic risk factors fully attenuated
- Suggests that obesity may play a mechanistic role in explaining links between reproductive aging and cardiometabolic risk


Reproductive Aging and Premenopausal Cardiovascular Risk

- The cross-sectional design limits conclusions regarding the direction of association between AMH and cardiometabolic risk factors
- Accelerated reproductive aging, as indexed by AMH, may be a risk factor for the promotion of CVD risk in the premenopausal period
- Cardiometabolic risk factors may also influence ovarian reserve


Premenopausal AMH is Associated with Subsequent Atherosclerosis

- Female Cynomolgus macaques (n=66)
- Treatment groups were balanced before treatment according to baseline AMH
- Premenopausal control (PRE)
- Ovariectomy (OVX)
- Reduced ovarian reserve (ROR)
- Measured plaque in iliac arteries

**Premenopausal AMH is Associated with Subsequent Atherosclerosis**

Conclusion
- A relationship exists between a marker of ovarian reserve (AMH) and atherosclerosis progression in monkeys

**Implement Class I Lifestyle Recommendations in All Women**
- Smoking cessation
- Heart healthy eating pattern
- Regular physical activity
- Weight management

**Effect of Early Menopause on Bone Mineral Density and Fractures**
- Cross-sectional studies show that early menopause, before age 45 years, leads to lower bone mass and increased osteoporosis
- A decade earlier than average menopause could reduce BMD by one T-score by age 65
- Early menopause is associated with increased fractures—reduced by estrogen Rx

**For Women At Risk Implement Class I Recommendations**
- Blood pressure control
- LDL therapy

**SWAN: Premature Menopause**
- Cross sectional survey of women aged 40 to 55 to determine eligibility
- POF reported in 1.1% of women
- Self-reported history of osteoporosis
  - OR*
    - All POI 3.7
    - Caucasian 5.6
    - African American 1.4 NS

Bone Health in Primary Ovarian Insufficiency

Hypogonadism in POI results in:
- Reduced rates of bone mass accrual in adolescents and young women
- > 90% peak bone mass achieved by age 18
- Low BMD for age in older women


Osteoporosis in POI: Diagnosis

- Bone density testing by DXA
- Z-score rather than T-score
- Z-score < -2.0
  - Low bone mineral density for chronological age
  - Below the expected range for age


Studies of POI and Low Bone Density

<table>
<thead>
<tr>
<th>Author</th>
<th>Date</th>
<th>Group</th>
<th>Osteopenia or Osteoporosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anasti</td>
<td>1998</td>
<td>NIH POH</td>
<td>2/3 had FN BMD &gt;1 SD below ref.</td>
</tr>
<tr>
<td>Bachelot</td>
<td>2009</td>
<td>Study Group</td>
<td>Reduced in POI</td>
</tr>
<tr>
<td>Uygur</td>
<td>2005</td>
<td>POF vs control group</td>
<td>Low BMD spine/ fem neck</td>
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<tr>
<td>Leite-Silva</td>
<td>2009</td>
<td>POI vs control</td>
<td>Low BMD at spine and hip</td>
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</tbody>
</table>


Early Menopause and Fracture Risk?

- Study of Osteoporotic Fracture
  - Mean age menopause: surgical 44 vs natural 49
  - Long-term risk of nonvertebral fracture is not increased for postmenopausal women s/p surgical menopause*
- Women’s Health Initiative Observational Study
  - BSO was not associated with increased risk of hip fracture compared to women with hysterectomy alone*

*Even in the absence of estrogen therapy.

Bone Health Primary Ovarian Insufficiency

Measures to optimize bone density
- Attention to lifestyle measures
- Resistance training
- Adequate calcium and vitamin D
- Replacement of estrogen/progestin
- Early implementation following diagnosis
- Adherence to therapy


Estrogen Therapy Primary Ovarian Insufficiency

- Transdermal estradiol preparations (100 mcg dose) may be superior to oral therapies
  - Does not suppress IGF-1
  - Lower risk of VTE
- Progestogen therapy (cyclical)
  - MPA 5-10 mg
  - Micronized progesterone 200 mg
- If delayed withdrawal bleed, D/C and pregnancy test

**Estrogen and POI: How long to treat?**

**NAMS 2012 HT Position Statement**

- "Unless contraindicated, women experiencing an early menopause who require prevention of bone loss are probably best served by the administration of HT or oral contraceptives, rather than other bone-specific treatments, until they reach the normal age of menopause at which time treatment may be reassessed."


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**When Ovaries Retire Too Soon Summary and Conclusions**

- Primary ovarian insufficiency, premature menopause, and early menopause represent different points along a continuum of ovarian function
- While fine points of diagnosis are relevant to distinguishing one etiology of POI from another, the dominant health concerns of the patients are similar
- After fertility issues have been addressed, it is essential to focus on symptom relief and long-term preventive strategies

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**When Ovaries Retire Too Soon Summary and Conclusions**

- Clinical trials to substantiate recommendation for patient management are lacking
- In the absence of data, clinical expertise dictates standard of care
- For women without contraindications, estrogen therapy relieves symptoms, prevents bone loss, and may be beneficial for overall health preservation

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**When Ovaries Retire Too Soon Summary and Conclusions**

- Therapy can be continued until the time of natural menopause, then reassessed
- Beyond emphasizing preventive strategies for cardiovascular and bone health, attention to mental wellbeing is also essential
- Improved strategies for care of these women may arise through international collaborative efforts including patient registries, international databases and multidisciplinary research efforts