Peri-Menopause and Menopause
Gary S. Donovitz, M.D., F.A.C.O.G

Peri-Menopause
• Perimenopause means "around menopause" and refers to the time period during which a woman's body makes its natural transition toward permanent infertility (menopause).

Menopause
• Menopause is defined as occurring 12 months after your last menstrual period and marks the end of menstrual cycles. Menopause can happen in your 40s or 50s, but the average age is 51 in the United States.

Traditional Definition But Not Practical
Why Does Menopause Matter?

- 100 years ago menopause was the end of lifespan
- 50 years ago women lived 20 years after menopause
- Now the post-menopause life has increased by 30+ years
- How do we optimize those 30+ years

**Same for Andropause**

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**HEALTHY LIFE EXPECTANCY**

22/23

**Industrialized Nations**

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**Hopkins Medicine**

- Wen Shen M.D.
- Graduated 1987 Johns Hopkins

- "Too Few doctors are prepared to help guide women through menopause...."
- "Hopkins never prepared me for the problems her patients were facing..."
A.C.O.G. Position Statement

“In response to recent media attention being given to so-called bioidentical hormones, The American College of Obstetricians and Gynecologists (ACOG) reiterates its position that there is no scientific evidence supporting the safety or efficacy of compounded bioidentical hormones.”

N.A.M.S. Position Statement 2012

“The risk of side effects (such as heart attack, stroke, blood clot, or breast cancer) with HT in healthy women ages 50 to 59 is low. In contrast, using HT for a long time or starting HT when you are a number of years beyond menopause is associated with a higher risk of these side effects.”
BHRT Cardio protective

- Transdermal E2 does not increase risk of VTE like oral E2
- Cardioprotective, decreased risk of AMI
- Decreased risk of T2DM
- Micronized P4 reduces risk of T2DM, does not increase risk of VTE, reduces BP

Best Outcome!

- Right Hormone (Bio-Identical)
- Right Dose (BioTE® Dosing Site)
- Right Route Of Administration (Sub Q)

W. H. I.- Worst Outcome!

- Wrong Estrogen
  - CEE is not a human hormone
  - Mostly Equillin
  - Low Estradiol (E2)
- Wrong “Progestrone”
  - MPA blocks progesterone receptors and is not a human hormone. MPA reverses benefits of E2
  - Wrong route
  - Oral Estrogens increase inflammation
  - Wrong women
  - Older (mean 63 years) who may already have established CV disease or breast cancer
Conventional HRT Women’s Health Initiative Trial

- 41% increase in stroke
- 29% increase in heart attacks
- 26% increase in breast cancer
- Twice the rate of blood clots
- 76% Increase in Alzheimer’s Dementia

**Note:**
After this trial many women were left with NO alternative for hormone balance and symptom relief. Sadly, there have been safe, alternative methods available for years.

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The new Mayo Clinic study combines the data from 43 randomized, controlled trials on hormone therapy. The trials included more than 52,000 women. All were 50 or older. The researchers found that neither of the main hormone therapies – estrogen alone, or estrogen combined with progesterone – affected a woman’s risk of dying from any cause, or specifically from a heart attack, stroke, or cancer.
Conventional HRT
Women’s Health Initiative Trial
In less than 2 years, half of the women who were using systemic hormone therapy stopped the treatment. Compared with 2001, use of oral estrogen-only among women aged 50-59 years with no uterus dropped by almost 60% in 2004, 71% by 2006, and 79% in 2010 and 2011, the authors noted.
In 2004 and 2011, they restated their data and said the mortality was lower in Estrogen users but the trend continues.
JAMA 2011;305:1305-14

The Mortality Toll of Estrogen Avoidance- Yale Study
Analysis of the 2011 WHI-ET (Women’s Health Initiative Estrogen-Alone Trial) data, showing that a minimum of 18,600 and as many as 91,600 excess deaths occurred between 2002 and 2011 among hysterectomized women aged 50-59 years due to ET avoidance.
Am. J. Public Health 2013

Which Diseases Has HRT Been Shown to Be Protective Of?
• Coronary Artery Disease
• Alzheimer’s Disease
• Dementia
• Strokes
• Degenerative Arthritis
• Osteoporosis
• Sexual Dysfunction
• Macular Degeneration
• Breast Cancer
• Colon Cancer
• Prostate Cancer
Positive Effects of Bio-identical Testosterone

**WOMEN**
- Enhanced libido
- Heart Protection
- Lower cholesterol and LDL
- Increased energy
- Enhanced sleep
- Feeling of overall well-being
- Reducing body fat
- Stronger bones and muscles
- Depression relief
- Reduced “brain fog”

*Minimal side effects for either men or women*

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Tx the Patient NOT the Lab

“Clinical manifestations of testosterone deficiency do not occur at a definitive threshold value”

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Women with Low T

- Increased risk for Alzheimer’s Disease
- Increased Risk for CVD
- Increased Risk for ORF
- Increased Risk for DM
- Possibly Breast Cancer
Top Ten Myths about Testosterone in Women

• Testosterone is a Male Hormone
  • Where is the AR located???
• Testosterone's only role in women is sex drive and libido
• Testosterone masculinizes women
  • Requires 30x dose we use
• Testosterone causes hoarseness and voice changes
  • Only true of anabolics
• Testosterone causes hair loss

Top Ten Myths about Testosterone in Women (cont.)

• Testosterone has adverse effects of the heart
• Testosterone causes liver damage
  • 3 reported cases hepatocellular carcinoma from oral synthetic T
• Testosterone causes aggression
• Testosterone may increase the risk of breast cancer
• The safety of testosterone use in women has not been established

Effect on Lipids
How about Low Fat Diet Effect on Cholesterol?

Effects of low-fat diets on TC, HDL-C and LDL-C only showed significant reductions in premenopausal women.
Osteoporosis

- Approximately one in seven women over age 50 has osteoporosis
- About one half of all women over age 50 can be expected to suffer an osteoporosis-related fracture during their lifetime
- After a hip or vertebral fracture, direct and indirect mortality can be as high as 25–30%
- All postmenopausal women should be advised to consume adequate amounts of calcium and vitamin D
- Treatment is recommended if the T-score is less than -2.5
- DXA screening should start at age 65

A.B.O.G 2014 MOC

*Am Journal OB/GYN* 163, 1474-1479

1. Testosterone: “Bone Builder”
2. Demonstrated Four-fold Increase in Bone Density vs. Oral Estrogen and 2.5x Greater than Patches
   - 8.3% per/year for Pellet Therapy
   - 3.5% per/year for Patches
   - 1-2% per/year for Oral Estrogen

Vertebral Fracture Risk Reduction Proportional to Hip BMD Change*

* Analysis of summary statistics from the FIT Trial

Hochberg M, Arthritis & Rheum. 1999;41:1306-14
SSRIs and Fractures

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
<th>Weight, % (random effect)</th>
<th>Relative Risk (95% CI)</th>
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<tbody>
<tr>
<td>Cohort</td>
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<tr>
<td>Schneeweiss and Wang 2004β</td>
<td>9.89</td>
<td>1.00 (1.54-2.10)</td>
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<tr>
<td>Richards, et al. 2007γ</td>
<td>4.87</td>
<td>3.16 (1.30-2.46)</td>
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<td>Lewis, et al. 2007δ</td>
<td>3.33</td>
<td>1.65 (9.93-2.34)</td>
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<tr>
<td>Ziere, et al. 2009ε</td>
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<td>2.39 (1.32-4.16)</td>
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<tr>
<td>Speight, et al. 2006ζ</td>
<td>10.09</td>
<td>1.36 (1.36-1.45)</td>
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<tr>
<td>Case Control</td>
<td>16.88</td>
<td>2.40 (2.13-2.70)</td>
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<tr>
<td>Liu, et al. 1998ι</td>
<td>16.66</td>
<td>1.42 (1.28-1.56)</td>
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<td>Hedlund, et al. 2003κ</td>
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<td>Vestergaard, et al. 2006λ</td>
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<td>Bottom, et al. 2008μ</td>
<td>9.24</td>
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<tr>
<td>van den Brand, et al. 2009ν</td>
<td>10.01</td>
<td>1.95 (1.84-2.06)</td>
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<tr>
<td>Overall</td>
<td>100.00</td>
<td>1.72 (1.51-1.95)</td>
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</tbody>
</table>

NOTE: The 1988–1994 estimates for men are considered unreliable because the estimates have relative standard errors of 20%–30%.

SOURCE: CDC/NCHS, Health, United States, 2013, Figure 25. Data from the National Health and Nutrition Examination Survey.
Early MCI

- Dementia takes 15-20 years to develop and begins with MCI (Mild Cognitive Impairment)
- MCI begins in the 30s-40s
- By 80-85, 50% of Americans have dementia
- Dementia may be accelerated by hormonal and neurotransmitter imbalances

HRT and Neurodegenerative Conditions

- HRT and particularly ERT plays an efficacious role in preventing neurodegenerative conditions
- E2 (17B Estradiol) can reduce the risk for Alzheimer’s disease and minimize cognitive decline in otherwise healthy women
- E2 can protect against B-amyloid induced degeneration
- Progestins may actually dampen this affect
- Compared to non-users E2 used for avg. 15 years had increased cerebral blood flow


HRT and Neurodegenerative Conditions

- Silverman et al looked at 17B Estradiol vs C.E.E. vs C.E.E. plus progestin on cerebral metabolic activity!
- Which one performed the best especially on verbal memory? 17B Estradiol 3 s.d. higher
- Verbal Memory is predominant symptom of ????

Early A.D.

Psychoneuroendocrinology 2010;36:502-513
Alzheimer's Disease

- Number of Alzheimer's cases will triple by 2050
- Cost will increase 500% to 1.1 trillion dollars
- Alzheimer's patients spend 3x more on health care cost than other patients
- Several Trials are under way to try and prevent the disease (SERM, SARMS)

Neurology 2/2013
Journal of Alzheimer's and Dementia 2/2013

Alzheimer's Disease

- Both Estrogen and Testosterone have Neuroprotective role
- Women have a higher incidence of AD 8:1 over men
- Women with lower E2 levels have even greater risk of AD
- There is overwhelming evidence that E and T helps decrease apoptosis
- This protective effect of both hormones decreases the beta amyloid deposition


Gonadal Sex Steroids

- ANTIOXIDANT
- ANTI-INFLAMATORY
- ANTIAMYLOIDGENIC

Antioxidants and Redox Signaling 2006
Vol 8, 2007
Alzheimer’s disease and HRT

THE HEART

Cardiovascular Disease

- Leading cause of morbidity and mortality in the United States
- Affects 12 million people
- 1 million deaths per year

JCEM 2005;90:6257-62
1 in 7 Premenopausal Women Die...

HEART DISEASE

For Postmenopausal Women that Number RISES to 1 in 3!

More Fatal Than Any Other Disease

- Heart disease is the leading cause of death of American women, killing more than a third of them.
- More than 200,000 women die each year from heart attacks, five times as many women as breast cancer.

www.cdc.gov/women/lcod/2010

Women on Statins and HRT and CVD

- Classic case of perception vs reality
- Extrapolation of data from studies on men
- No evidence that statins reduce all cause mortality or are beneficial for primary prevention
- All cause mortality rates from 1992-1996 to 2002 to 2006 increased in 42% of U.S. counties, but increased in only 3.4% of U.S. counties for men.
- Among women on HT and statins 5/10,000 CV events if on statins only 18/10,000

Menopause 2015. 22:363-64
Menopause 2015.33: 369-76
Women on Statins and HRT and CVD

“It is important to be clear that HT reduces all cause mortality, whereas statin therapy does not in primary prevention. Avoidance of HT is associated with excess morbidity and mortality.”

Menopause 2015. 22:363-64

Estrogen Replacement and Coronary Artery Disease

Effect on Survival in Postmenopausal Women

Effects of HRT on CV Events in Recent Post-Menopausal Women: Randomized Trial

• 1006 women, 45-58 y.o., recently post-menopausal
• Treated with 17 Beta Estradiol and norethindrone if they had uterus
• After 10 years: 16 women had CV event in treatment group vs 33 in control group (HR .48, C.I. .26-.87)
• No increase risk of Breast cancer or DVT or stroke
• After 16 years the protection was still present

BMJ 2012;345:e6409
Aromatase Extremes and CV Mortality in Older Women

- Prospective Study 809 women over 50 y.o. not using Estradiol
- Aromatase Index (estrone /androstenedione) measured and patients followed for 14 yr
- 49% of deaths due to CV Disease
- Highest and Lowest Quintiles were positively associated with CVD mortality (nearly double the middle quartiles)
- Age and B.M.I. are positively associated with aromatase activity

Clinical Endocrinology
2012;77:391-98

BREAST CANCER

- Most Common female cancer
- Median age 61 y.o.
- 400,000 deaths annually worldwide
- 75% occur in postmenopausal women
- 80% are hormone receptor positive
- How long do they use adjuvant therapy?
- What percent reoccur in years 5-15 after dx?
WHI Estrogen Alone

<table>
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<th>Outcome</th>
<th>HR</th>
<th>Nominal CI</th>
<th>Adjusted CI</th>
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<td>CHD</td>
<td>0.85</td>
<td>0.79-1.16</td>
<td>0.76-1.19</td>
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<td>Stroke</td>
<td>1.19</td>
<td>1.15-1.22</td>
<td>0.97-1.09</td>
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<td>Breast Cc</td>
<td>0.77</td>
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<tr>
<td>Total Fx</td>
<td>0.70</td>
<td>0.63-0.79</td>
<td>0.59-0.83</td>
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</tbody>
</table>

*p=0.1, controls adjusted data.

1. High CV et al. (2000) JAMA 283 352-363

Review of Studies Published From 1975-2000: Lack of Consistent Results ET and Breast Cancer Risk (45 Studies)

- 82% of studies reported risk estimates not significantly different from 1.0
- 13% of studies reported risk estimates > 1.0, but none > 2.0
- 2% of studies reported risk estimates < 1.0


Reduced breast cancer incidence in women treated with subcutaneous testosterone, or testosterone with anastrozole: A prospective, observational study

<table>
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<th>DRF</th>
<th>Median age (years)</th>
<th>50th percentile</th>
<th>75th percentile</th>
<th>75th percentile</th>
<th>Median age at first T insertion</th>
<th>Age at time of analysis for comparison to SEER database</th>
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<td>WHI ET</td>
<td>4.35</td>
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<td>87.5</td>
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<td>Test arms</td>
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<td>Patients</td>
<td>570</td>
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<td>87.5</td>
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<td>Adenoma</td>
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<td>87.5</td>
<td>57.0</td>
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<td>Adenoma (2010)</td>
<td>50.8</td>
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<td>87.5</td>
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<td>87.5</td>
<td>87.5</td>
<td>57.0</td>
<td>71</td>
</tr>
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</table>

*Median age at time of analysis for comparison to SEER database.
Dayton Experience-82 month data-January 2015

- 4 cases of invasive BCA in 5231 p-y of therapy
- Incidence of 76/100 000 p-y
- SEER expected incidence 297/100 000 p-y

10th European Congress on Menopause and Andropause 5/2015

Dr. Donovitz 2008-2014

- 41,000 insertions
- 20% males
- 80% females
- Total Females= 32,800 insertions
- Avg Frequency 3.6 months
- Therefore 9,111 female patients
- Total 9 breast cancers, 0 mortality

E/P Arm of W.H.I.

- 38 developed breast cancer each year, compared to 30 breast cancers for every 10,000 women taking a placebo each year
- There was no difference in the development of breast cancer during the first 4 years among women taking estrogen plus progestin, compared to those taking a placebo. After that time, the numbers began to increase. After an average of 5.2 years, there was an increased risk of breast cancer in women taking estrogen plus progestin compared to those taking placebos.
- 34 had blood clots in the lungs or legs, compared to 16 out of every 10,000 women taking a placebo
Hormone Replacement Therapy After a Diagnosis of Breast Cancer in Relation to Recurrence and Mortality

- 2755 women age 35-74
- The rate of breast cancer recurrence was 17 per 1000 person-years in women who used HRT
- 30 per 1000 person-years in nonusers
- Breast cancer mortality rates were five per 1000 person-years in HRT users and 15 per 1000 person-years in nonusers
- Total mortality rates were 16 per 1000 person-years in HRT users and 30 per 1000 person-years in nonusers


Matrix Metalloproteinase-9

- If MMP-9 is increased in stroma worse prognosis
- Degrades extracellular matrix enabling tumor invasion
- Increased metastatic disease
- Increased angiogenic activity

Clin Cancer Res 2004;10: 7621
Breast Ca Res Treat 2007;102:253-61

Management (a.k.a. Traditional Therapy)

WOMEN
- Premarin, Enjuvia, Estradiol, etc.
- Vivelle
- Synthetic Estrogen and Testosterone injections
- Sub-cutaneous Pellet Both E2 and T
Potential and Unnecessary Effects of Oral Estrogen Therapy Continued

- SHBG
- CBG
- TBG
- CRP, IL-6, MMP-9

Provocative Thoughts of the Day

- Is lowering BP to extremely low levels good for the patient?
- Where is the data that lowering cholesterol is so beneficial?
- Do mammograms save lives or increase mastectomies?
- Is hormone optimization the key to improving quality of life?
- If we continue to over-diagnose won't we make people sicker not healthier with drugs and tx we use?