Hormone Replacement Therapy (HRT)
Menopausal hormone therapy (MHT)

Has emotion overtaken reason?

Lily Agrawal, M.D., FACE
We will discuss...

- Definition & scope of menopause
- Major trials of HRT
- Risks in specific populations
- Regimens commonly used
- Conclusions

I have no disclosures
Reproductive hormones in women

Estrogens

- 17β estradiol (E2)
  - most bioactive
  - primarily produced by dominant ovarian follicle & corpus luteum
- Estrone (E1)
  - primarily derived from metabolism of E2
    - also from aromatization of androstenedione, ovarian & adrenal secretion
- Estriol (E3)
  - least active

Progesterone

- secreted by ovary, not produced after menopause.

Testosterone

- produced by ovary, adrenal cortex, & peripheral conversion of androstenedione & DHEA.
Declining follicle number with age

A comparison of the relationship between age and primordial follicle number in Block's study of 44 girls and women aged 7 to 44 years with that of Gougeon's study of women aged 45 to 55 years. Follicle depletion appears to accelerate in the decade preceding menopause.

Factors determining age at menopause

- Genetics
  - Genetic variation in the estrogen receptor gene
- Family history
  - Earlier in women with a family history of early menopause
- Ethnicity
  - Compared to Caucasian women, occurs earlier in Hispanic women and later in Japanese-American women
- Smoking
  - Occurs ~2 yrs earlier in women who smoke
- Reproductive history
  - Earlier in women who are nulliparous or who had shorter cycle length during adolescence
Patient histories...

- 56 yr WF with regular menses who c/o hot flashes x 1yr, “1 minute I’m an energizer bunny & then I’m drained of all energy”, inability to stay asleep, lack of sexual desire. Normal CBC, CMP, TFT.

- 61 yr WF s/p hysterectomy (~2003) 2/2 possible ovarian cancer per patient, DM 2, osteoporosis->s/p T-12 vertebroplasty (on calcium, vitD, forteo), hyperlipidemia, myasthenia gravis (on prednisone, imuran), s/p CABG, sinus tachycardia, asthma, depression, non-smoker. Very bothered by profuse sweating, constantly wiping sweat off her face & body. TFT, IGF-1, catecholamines, 5-HIAA normal, estradiol v low.

- 73 WF s/p hysterectomy in her 30’s for prolapse-ovaries were left in, osteopenia, CVA? '04 (unclear history, had brady & postural hypotension req pacemaker, no deficits), h/o CAD(cath in '02 showed 80% RCA ostial lesion, medical Mx), paroxysmal atrial fibrillation->pacemaker, dyslipidemia, hypothyroid, asthma, hiatal hernia-> s/p Nissen procedure, insomnia, nephrolithiasis, non-smoker. She was on ERT until 2002 when it was stopped because of negative publicity. Since then she has muscle & bone aches, hot & cold flashes, excess sweating & feels that her whole life would improve with return of HRT.
MOOD SWINGS CAUSED BY THE MENOPAUSE AREN'T HELPED BY SUGGESTIONS

If you feel like shouting, just close your eyes and count to ten!

"What do you mean you know how I feel? Like you’ve had a hell of a day with your hormones!"
### Symptoms of menopause

<table>
<thead>
<tr>
<th>Good evidence</th>
<th>Fair evidence</th>
<th>Poor evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasomotor symptoms (hot flashes and night sweats)</td>
<td>Depression, anxiety, and/or irritability</td>
<td>Back pain, tiredness, and stiff or painful joints. Wrinkling/dry skin. Change in body composition.</td>
</tr>
<tr>
<td>Vaginal dryness and painful intercourse</td>
<td>Changes in libido, arousal, and other aspects of sexuality</td>
<td>Urinary incontinence</td>
</tr>
<tr>
<td>Sleep disturbance, palpitations</td>
<td>Difficulty thinking, forgetfulness, or other cognitive disturbances</td>
<td>Positive or negative effects on quality of life</td>
</tr>
</tbody>
</table>
90% physicians say they are comfortable talking to their patients about menopause

50% women 45-60yr age have some s/s; 1/3rd have mod-severe s/s.
~50% of all women (and their physicians) have a negative impression of HRT

70% of symptomatic women have not received any Rx; 60% have not discussed with their doctor.

<25% had considered HRT to Rx s/s.
<20% report receiving Rx for s/s

~10% have a positive impression of HRT
Menopausal Hormone Treatment

- Prevents or abolishes hot flashes
- Prevents or improves vaginal atrophy
- Prevents or slows bone loss
- Reduces risk of heart disease
- Improves blood flow to brain
- May reduce risk of Alzheimer’s disease
- May reduce risk of colon cancer
- Improves overall quality of life
A = meta-analysis of 31 observational studies of estrogen use and CHD risk
B = meta-analysis of 32 observational studies of estrogen use, including 3 studies of estrogen-progestin use, and CHD risk
C = Nurses' Health Study, 10-year follow-up of estrogen use and CHD risk
D = Nurses' Health Study, 16-year follow-up of estrogen-only use and CHD risk
E = Nurses' Health Study, 16-year follow-up of estrogen-progestin use and CHD risk
F = HERS prospective, randomized study of estrogen-progestin use for secondary prevention of CHD
Why are we still talking about this?

- Observational studies since the 1960’s showed HRT reduced cardiovascular disease and mortality when used around menopause.
- Study biases:
  - healthy-user bias
  - compliance bias
  - surveillance bias
  - healthy-survivor bias
- After Women’s Health Initiative (WHI, 2002), everyone said, ‘hormones are killing women!’
- They do have risks, but they are low, and certainly no higher than many other drugs we use.
The clinical use of estrogens to treat menopausal symptoms was first evaluated in the late 1920’s. In 1942, FDA approved Premarin as the most effective medicine to alleviate menopausal symptoms.

By 1990s, ~1/3 menopausal women were taking HRT.

In 2003–2004, a sharp decline occurred & overall prevalence decreased to 11.9% (mostly in Caucasian women).

Through 2009–2010, hormone use continued to decline across all patient demographic groups.

In 2012, prevalence is at 4.7% overall, 2.7% for estrogen only, and 1.7% for estrogen plus progestin.

Cross-sectional data from 10,107 women aged ≥40 years in the National Health and Nutrition Examination Survey. Sprague, Brian L. PhD; Trentham-Dietz, Amy PhD; Cronin, Kathleen A. PhD. Obstetrics & Gynecology: September 2012 - Volume 120 - Issue 3 - p 595-603.
Major HRT trials


- Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative (WHI) randomized controlled trial. JAMA. 2002;288(3):321

- Nurses Health Study (NHS), Study of Women’s Health Across the Nation SWAN), Women’s International Study of long Duration Oestrogen after Menopause (WISDOM), Early vs Late Intervention Trial with Estradiol (ELITE), Kronos Early Estrogen Prevention Study (KEEPS).
<table>
<thead>
<tr>
<th></th>
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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>875, healthy</td>
<td>2763, had documented CHD -&gt;secondary prevention trial</td>
<td>E2 + P = 16,608, healthy, intact uterus; E2 only = 10,739 s/p hysterectomy</td>
</tr>
<tr>
<td>Mean years of f/u</td>
<td>3 years</td>
<td>4.1 yrs</td>
<td>E2 + P=mean of 5.2 years (1993-2002); E2 only=Mean of 6.8 yrs (1993-2004)</td>
</tr>
<tr>
<td>Age</td>
<td>45-64 years (mean 56 years)</td>
<td>&lt;80 years (mean 66.7 years)</td>
<td>50-79 years (mean 63 years)</td>
</tr>
<tr>
<td>Hormone (s) used</td>
<td>CEE, 0.625 mg/d; CEE, 0.625 mg/d +cyclic MPA, 10 mg/d for 12 d/mo; CEE, 0.625 mg/d + consecutive MPA, 2.5 mg/d; CEE, 0.625 mg/d plus cyclic MP 200 mg/d for 12 d/mo; PBO.</td>
<td>CEE, 0.625 mg/d, +/- MPA, 2.5 mg/d. (prempro or placebo)</td>
<td>CEE, 0.625 mg/d, +/- MPA, 2.5 mg/d. (prempro or premarin)</td>
</tr>
<tr>
<td>E2 + P</td>
<td>Estrogen decreases LDL-C and increases HDL-c, lowers fibrinogen</td>
<td>No difference in heart disease, 11% lower LDL cholesterol, 10% higher HDL cholesterol, VTE 2.89 (1.50-5.58), gallbladder disease 1.38; decr diabetes; no significant differences in fracture, cancer, and total mortality</td>
<td>Estimated hazard ratios (HRs) CHD, 1.29 (1.02-1.63); breast cancer, 1.26 (1.00-1.59) stroke, 1.41 (1.07-1.85); PE, 2.13 (1.39-3.25); colorectal Ca, 0.63 (0.43-0.92); endometrial Ca, 0.83; hip fracture, 0.66 (0.45-0.98); death due to other causes, 0.92</td>
</tr>
<tr>
<td>E2 only</td>
<td>Unopposed estrogen is optimal regimen for elevation of HDL-C, but the high rate of endometrial hyperplasia restricts use to women without a uterus.</td>
<td></td>
<td>stroke, 1.39 (1.10-1.77); PE, 1.34 (0.87-2.06); colorectal cancer, 1.08 (0.75-1.55); CHD, 0.91 (0.75-1.12); breast cancer, 0.77 (0.59-1.01); hip fracture, 0.61 (0.41-0.91)</td>
</tr>
</tbody>
</table>

CEE=conjugated equine estrogens eg Premarin; PBO=placebo
MPA=medroxy progesterone acetate eg Provera; MP=micronized progesterone eg prometrium;
The National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) has stopped early a major clinical trial of the risks and benefits of combined estrogen and progestin in healthy menopausal women due to an increased risk of invasive breast cancer.

Embargoed for Release: July 9, 2002

In 2000 and 2001, the study informed participants of a small increase in heart attacks, strokes, and blood clots in women taking hormones. The actual number of women having any one of these events was small and it did not cross the statistical boundary.

In May 2002, the data review revealed for the first time that the number of cases of invasive breast cancer in the E+P group had crossed the boundary established.

It was felt that this is a relatively small annual increase in risk for an individual woman. Individual women who have participated in the trial and women in the population who have been on E+P should not be unduly alarmed. However, even small individual risks over time, and on a population-wide basis, add up to tens of thousands of these serious adverse health events.

WHI was scheduled to run until 2005, but it was stopped after an average follow-up of 5.2 years.
Women’s Health Initiative (WHI) and Risk

- WHI emphasized the *relative risk* of benefit or harm.
- For example, it reported that the *relative risk for breast cancer increased by 26%* for women taking combined hormone therapy (E₂ + P) for an average of 5.2 years, compared with women who did not.
- That does not mean you have a 26%, or 1 in 4 chance of getting breast cancer if you take HRT.
- A group of 1000 women who do not take hormones.
  - Out of that group, 18 women will develop breast cancer in 5 years.
  - If those 1000 women take combined hormone therapy for 5 years, and their relative risk increases by 26%, ~4 more cases.
  - 22 out of 1000 with combined hormone therapy, compared with 18 out of 1000 without hormone therapy. That means your excess or added risk is 4 in 1000.
- When considering the risks of hormone therapy, it is helpful to focus on *excess risk*, or the number of additional cases, and not the *relative risk*, or the percentage.
Excess risk, if 10,000 postmenopausal women took hormone therapy* for one year

<table>
<thead>
<tr>
<th>Estrogen and Progestin</th>
<th>Estrogen Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 more VTEs</td>
<td>7 more VTE</td>
</tr>
<tr>
<td>7 more CHD Events</td>
<td>5 fewer CHD events</td>
</tr>
<tr>
<td>8 more strokes</td>
<td>12 more strokes</td>
</tr>
<tr>
<td>8 more invasive breast cancers</td>
<td>7 fewer breast cancers</td>
</tr>
<tr>
<td>8 more PEs</td>
<td>3 more PEs</td>
</tr>
<tr>
<td>6 fewer colorectal ca</td>
<td>1 more colorectal ca</td>
</tr>
<tr>
<td>5 fewer hip fractures</td>
<td>6 fewer hip fractures</td>
</tr>
</tbody>
</table>

*Using CEE and MPA
Danish Osteoporosis Prevention Study (DOPS)

- 1006 postmenopausal women
- mean age of ~50 years
- used HRT for ~10 years (then followed for 6 more years → 20,000 women-years of follow-up).
- 2-mg synthetic 17β estradiol for 12 days,
  2 mg 17β estradiol + 1 mg norethindrone acetate for 10 days, and 1 mg 17β estradiol for 6 days.
- Limitations: small size, different drug regime; but follow-up is longer than the WHI on a trial and post-trial surveillance.

Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial (Published 9 October 2012) BMJ 2012;345:e6409
### Results After 10 Years of Intervention in Danish Osteoporosis Prevention Study (DOPS)

<table>
<thead>
<tr>
<th>End point</th>
<th>HRT group (n=502), n</th>
<th>Control group (n=504), n</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary&lt;sup&gt;a&lt;/sup&gt;</td>
<td>16</td>
<td>33</td>
<td>0.48</td>
<td>0.26–0.87</td>
<td>0.015</td>
</tr>
<tr>
<td>Mortality</td>
<td>15</td>
<td>26</td>
<td>0.57</td>
<td>0.30–1.08</td>
<td>0.084</td>
</tr>
<tr>
<td>Cancer</td>
<td>36</td>
<td>39</td>
<td>0.92</td>
<td>0.58–1.45</td>
<td>0.71</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>10</td>
<td>17</td>
<td>0.58</td>
<td>0.27–1.27</td>
<td>0.17</td>
</tr>
<tr>
<td>DVT</td>
<td>2</td>
<td>1</td>
<td>2.01</td>
<td>0.18–22.16</td>
<td>-&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stroke</td>
<td>11</td>
<td>14</td>
<td>0.77</td>
<td>0.35–1.70</td>
<td>0.70</td>
</tr>
</tbody>
</table>

<sup>a</sup>. 50% reduction in cardiovascular end points—significantly reduced risk of the combined end point of death, MI, or heart failure.  
No significant increased risk of breast cancer, stroke, DVT or PE.  
<sup>b</sup>. Numbers too low to calculate p
Kronos Early Estrogen Prevention Study (KEEPS)

- 727 women,
- Ages 42-59 yrs (mean 52), within 3 years after menopause (healthy women in early menopause).
- Treated for ~4 years.
- Exclusion—evidence of CV disease, levels of cholesterol that would normally be treated with lipid-lowering drugs, severe obesity, heavy smoking.

<table>
<thead>
<tr>
<th>First group</th>
<th>Second group</th>
<th>Third group</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.45 mg a day of Premarin (an oral CEE)</td>
<td>50 μg a day of transdermal estradiol (Climara patch)</td>
<td>placebo E2 &amp; P</td>
</tr>
</tbody>
</table>

+ 200 mg of micronized progesterone (Prometrium) for 12 days/month.

- Results—Reduced hot flashes and night sweats, favorable effects on BMD, improved sexual function, trend towards reduced Coronary artery calcium score.
- No statistically significant differences in BP, rates of breast cancer, endometrial cancer, myocardial infarction, TIA, stroke, or VTE.

Manson JE, et al "New findings from the Kronos early estrogen prevention study (keeps) Randomized trial" NAMS 2012. study was sponsored by the Kronos Longevity Research Institute with private funding from the founder of University of Phoenix & funding from the National Institutes of Health
### Summary of 9 HRT trials 2002–2012

<table>
<thead>
<tr>
<th>Outcome</th>
<th>E₂+P vs toPBO</th>
<th>E₂+P vs PBO</th>
<th>E₂ vs PBO</th>
<th>E₂ vs PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
<td><strong>Hazard ratio</strong></td>
<td><strong>Diff in events per 10,000 women years (95% CI)</strong></td>
<td><strong>Hazard ratio</strong></td>
<td><strong>Diff in events per 10,000 women years (95% CI)</strong></td>
</tr>
<tr>
<td>Invasive breast Ca</td>
<td>1.25</td>
<td>8 more (3-14)</td>
<td>0.77</td>
<td>8 less (1-14)</td>
</tr>
<tr>
<td>Lung Ca</td>
<td>1.23</td>
<td></td>
<td>1.17</td>
<td></td>
</tr>
<tr>
<td>Colorectal Ca</td>
<td>0.75</td>
<td>6 less</td>
<td>1.11</td>
<td>1 more</td>
</tr>
<tr>
<td>Endometrial Ca</td>
<td>0.78</td>
<td></td>
<td>n/a (no uterus)</td>
<td></td>
</tr>
<tr>
<td>MI/death from CAD</td>
<td>1.22</td>
<td>7 more</td>
<td>0.95</td>
<td>5 less</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.34</td>
<td>9 more (2-15)</td>
<td>1.36</td>
<td>11 more (2-20)</td>
</tr>
<tr>
<td>DVT</td>
<td>1.88</td>
<td>12 more (6-17)</td>
<td>1.47</td>
<td>7 more (1-14)</td>
</tr>
<tr>
<td>PE</td>
<td>1.98</td>
<td>9 more (4-14)</td>
<td>1.37</td>
<td>3 more</td>
</tr>
<tr>
<td>Diabetes, new Dx</td>
<td>0.79</td>
<td>15 less (4-26)</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>Total fractures</td>
<td>0.76</td>
<td>46 less</td>
<td>0.70</td>
<td>56 less</td>
</tr>
<tr>
<td>Gall bladder disease</td>
<td>1.61</td>
<td>20 more (11-29)</td>
<td>1.79</td>
<td>33 more (20-45)</td>
</tr>
<tr>
<td>Probable dementia</td>
<td>2.05</td>
<td>22 more (5-39)</td>
<td>1.49</td>
<td></td>
</tr>
</tbody>
</table>

[http://www.uspreventiveservicestaskforce.org/uspstf12/menohrt/menohrtartaptab.htm](http://www.uspreventiveservicestaskforce.org/uspstf12/menohrt/menohrtartaptab.htm). It includes the 2 main WHI trials, 2 trials consisting of subsamples from the WHI trials (WHIMS and WHISCA), EMS, HERS, ESPRIT, ULTRA trial, and WISDOM.
Risks and benefits of HRT

Early menopause (1st 5 yrs after final period)

**Benefits include:**
- Relief of hot flashes, vasomotor s/s
- Relief of symptoms of urogenital atrophy
- Prevention of fractures
- Prevention of diabetes.
- Reduction of overall mortality
- Reduction of CHD and total MI
- Beneficial effects on colorectal and endometrial cancer

**Risks include:**
- Venothrombotic episodes,
- Stroke (tho’ small risk)
- Cholelithiasis/cystitis.
- Estrogen plus some progestogens increased the risk of breast cancer
- Estrogen alone did not increase the risk of breast cancer
- Data from the various WHI, which involved women of average age 63, cannot be appropriately applied to calculate risks and benefits of HRT in women starting shortly after menopause.

Late menopause (from 5 yrs till end of life)

**Benefits include:**
- Relief of hot flashes, vasomotor s/s
- Relief of symptoms of urogenital atrophy
- Beneficial effects on colorectal and endometrial cancer

**Risks include:**
- Venothrombotic episodes,
- Stroke
- Possible initial increase in CHD; estrogen alone did not increase the risk of CHD
- Breast cancer; estrogen alone did not increase the risk of breast cancer
- Did not prevent/may increase dementia
Bioidentical hormones

**Prescription regulated**
- Chemically identical to human hormones
- US FDA oversight
- Published scientific research
- Doses exactly reproducible
- Proven efficacy

**Customized compounded**
- Chemically identical to human hormones
- No US FDA oversight
- Minimal to no published scientific research
- Doses may be inexact & inconsistent
- Efficacy & safety not proven in randomized trials, hence not recommended

Cleveland Clinic Journal of Medicine December 2001; Vol 78 (12) 829-836
Estrogen preparations available

<table>
<thead>
<tr>
<th></th>
<th>conjugated equine estrogens (CEE)</th>
<th>Steroidal estrogens</th>
<th>Non steroidal estrogens</th>
</tr>
</thead>
</table>
| Estrogen contained     | mostly estrone sulfate + small amounts of equilin sulfate, dihydroequilin sulfate, and many other estrogens | 1. micronized 17-beta-estradiol  
2. Ethinyl estradiol (v potent)  
3. Estropipate/piperazine  
4. parenteral preps | Phytoestrogens: isoflavones, polyphenols, coumestans, and lignans                      |
| Derived from           | pregnant mares' urine             | plant sources (soy and yams)                                                     | soybeans, chickpeas, lentils, flaxseed, grains, fruits, and vegetables                  |
| Preparations available | Premarin (0.3, 0.45, 0.625, 0.9, 1.25 mg) | 1. Estrace 0.5, 1, 2 mg;  
2. Femhrt 2.5-5 ug of ethinyl estradiol (with 0.5 or 1 mg norethindrone acetate)  
3. Ogen, menest, ortho-est  
4. Patches-0.014, 0.025, 0.0375, 0.05, 0.1 mg/d(climara, vivelle), combipatch (E2 + P)  
   -vaginal preps-femring  
   -topical preps-estrasorb, divigel, estrogel. 0.25, 0.35, 0.5 & 1.0 mg/d  
   -topical skin spray-evamist 0.02mg/d | Found in ~60% of processed foods |
<table>
<thead>
<tr>
<th>Type/source</th>
<th>Brand name(s)</th>
<th>Preparations</th>
<th>Bioidentical?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Estrogens</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjugated equine estrogens (CEE)/pregnant mares’ urine</td>
<td>Premarin</td>
<td>Pill, Vaginal cream</td>
<td>No</td>
</tr>
<tr>
<td>Synthentic conjugated estrogens/plants</td>
<td>Cenestin, Enjuvia</td>
<td>Pill</td>
<td>No</td>
</tr>
<tr>
<td>Esterified estrogens/plants</td>
<td>Menest</td>
<td>Pill</td>
<td>No</td>
</tr>
<tr>
<td>17 beta-oestradiol/plants (micronized)*</td>
<td>Estrace, others</td>
<td>Pill</td>
<td>Yes**</td>
</tr>
<tr>
<td></td>
<td>Alora, Climara, Esclim, Estraderm, Vivelle, others</td>
<td>Patch</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Estrovel</td>
<td>Transdermal gel</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Estrasorb</td>
<td>Topical cream</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Estrace</td>
<td>Vaginal cream+</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Estring</td>
<td>Vaginal ring+</td>
<td>Yes</td>
</tr>
<tr>
<td>Estropipate (modified estrone)/plants</td>
<td>Ortho-Est, Ogen, others</td>
<td>Pill</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Ogen</td>
<td>Vaginal cream+</td>
<td>No</td>
</tr>
<tr>
<td>Estradiol acetate</td>
<td>Femring</td>
<td>Vaginal ring</td>
<td>Yes</td>
</tr>
<tr>
<td>Estradiol hemihydrate</td>
<td>Vagifem</td>
<td>Vaginal tablet+</td>
<td>Yes</td>
</tr>
<tr>
<td>Ethinyl estradiol</td>
<td>Estinyl</td>
<td>Pill</td>
<td>No</td>
</tr>
</tbody>
</table>
Estrogen preparations available (contd)

Oral estrogen administration increases hepatic production of:
- thyroxine-binding globulin,
- corticosteroid-binding globulin,
- sex hormone-binding globulin,
- triglycerides,
- high-density lipoprotein (HDL) cholesterol,
- clotting factors,
- saturation of bile with cholesterol

Transdermal estrogen administration:
- only minimally increased production of above
- lower risk of venous thrombosis and stroke
- Less effect on serum lipid concentrations

0.625 mg conjugated estrogen (premarin) or estrone sulfate
1.0 mg micronized 17-beta-estradiol (estrace)
50 mcg or 0.05 mg transdermal 17-beta-estradiol (climara)
5 mcg of ethinyl estradiol (Femhrt, an extremely potent synthetic estrogen)
1.25 mg piperazine estrone sulfate
### Progesterone preparations available

<table>
<thead>
<tr>
<th>Progestagen contained</th>
<th>Medroxy progesterone acetate (MPA, 17 OH progesterone)</th>
<th>Natural oral micronized progesterone</th>
<th>Progestins derived from testosterone (19 nortestosterone)</th>
<th>Drospirenone derived from 17 alpha-spironolactone</th>
<th>Levonorgestrel containing intrauterine device</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preps available</td>
<td>Provera 5-10 mg/day x 12-14 days/month cyclically; or 2.5 mg/d continuously</td>
<td>Prometrium 200 mg/day x 12 days/month cyclically; or 100 -200 mg/d continuously</td>
<td>Noretindrone 2.5mg x 12 days; Levonorgestrel</td>
<td>Drospirenone (0.5 &amp; 2 mg) and Estradiol (1 mg) has been commercially available in Europe</td>
<td>Mirena IUD. 20 ug of levonorgestrel per day (5 year use; not approved for menopause)</td>
</tr>
<tr>
<td>Properties</td>
<td>Have little androgenicity</td>
<td>Cause less attenuation of the favorable lipid profile induced by estrogen</td>
<td>Have more androgenic action, can lower HDL</td>
<td>has progestogenic, antiandrogenic, and antimineralo-corticoid activity</td>
<td></td>
</tr>
</tbody>
</table>

Side effects of progestogen can include anxiety, irritability, depressed mood, acne, bloating, fluid retention, headaches, breast tenderness, and bleeding problems.
### Progestins, micronized progesterone

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Preparation</th>
<th>Bioidentical?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medroxyprogesterone acetate (MPA)</td>
<td>Amen, Cycrin, Provera</td>
<td>Pill</td>
</tr>
<tr>
<td>Micronized* progesterone USP</td>
<td>Prometrium</td>
<td>Pill</td>
</tr>
<tr>
<td></td>
<td>Prochive 4%</td>
<td>Vaginal gel</td>
</tr>
<tr>
<td>Norgestrel</td>
<td>Ovrette</td>
<td>Pill</td>
</tr>
<tr>
<td>Norethindrone</td>
<td>Micronor, Nor-QD, others</td>
<td>Pill</td>
</tr>
<tr>
<td>Norethindrone acetate</td>
<td>Aygestin, others</td>
<td>Pill</td>
</tr>
</tbody>
</table>

### Combined hormones

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Preparation</th>
<th>Bioidentical?</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEE and MPA</td>
<td>Premphase, Prempro</td>
<td>Pill</td>
</tr>
<tr>
<td>Ethinyl estradiol and norethindrone acetate</td>
<td>Femhrt</td>
<td>Pill</td>
</tr>
<tr>
<td>17 beta-estradiol and norethindrone acetate</td>
<td>Activella</td>
<td>Pill</td>
</tr>
<tr>
<td></td>
<td>Combipatch</td>
<td>Patch</td>
</tr>
<tr>
<td>17 beta-estradiol and norgestimate</td>
<td>Prefest</td>
<td>Pill</td>
</tr>
<tr>
<td>17 beta-estradiol and levonorgestrel</td>
<td>Climara Pro</td>
<td>Patch</td>
</tr>
</tbody>
</table>

*Particles are made smaller for better absorption.
**Bioidentical estradiol until ingested and converted in the liver to estrone.
+For vaginal symptoms only.
++The estradiol is bioidentical but not the progestin.

Bioidentical estradiol in pill form is converted in the liver to estrone, a weaker bioidentical estrogen. But given in a patch, it enters the bloodstream as bioidentical estradiol. Creams, gels, and lotions applied to the legs or arms can also deliver bioidentical estradiol directly to the bloodstream, although it's uncertain how much is absorbed.
Common HRT regimens used

• **Premphase** (Premarin 0.625 mg/day + Provera 5-10 mg/day on days 1-13 or 14 of each month cyclically); or **Prempro** (Premarin 0.625 mg/day + Provera 2.5 mg/d continuously).

• **Daily estrogen** (oral or transdermal, continuously) with 200 mg natural progesterone (**prometrium**) on days 1-13 or 14 of each month.

• Daily estrogen (continuously) with progesterone for 14 days every 3 months for women who have difficulty tolerating progestin therapy (but associated with higher endometrial hyperplasia).

• Oral 0.25 mg of drospirenone and 0.5 mg of estradiol, or 0.5 mg of drospirenone and 1 mg of estradiol (**Angeliq**).

• Oral norethindrone acetate, ethinyl estradiol (0.5 mg/2.5 mcg or 1 mg/5 mcg (**Femhrt**).

• **ClimaraPro patch**/week=0.045 estradiol + 0.015 levonorgestrel.

• **CombiPatch**=estradiol + norethindrone acetate 0.05/0.14 or 0.05/0.25mg/day. Use as continous Rx twice a week or sequential Rx alternating CombiPatch and Vivelle-Dot (estradiol transdermal system).
Duration of use

- Use the lowest HRT/ET dose for the shortest period needed to alleviate s/s.
- Extending duration is acceptable if:
  - Benefits of menopause s/s relief outweigh risks
  - High risk of fracture & alternative bone specific therapies are not appropriate/acceptable
Contraindications to HRT

- **Absolute contraindications**
  - Undiagnosed **vaginal bleeding**
  - Pregnancy
  - Severe/active **liver disease**
  - Active **coronary artery disease** (CAD)
  - **Venous thrombosis**
  - Well-differentiated and early **endometrial cancer** (once treatment for the malignancy is complete, is no longer an absolute contraindication). Progestins alone may relieve symptoms if the patient is unable to tolerate estrogens.

- **Relative contraindications**
  - **Migraine** headaches
  - Personal history of **breast cancer**
  - Atypical **ductal hyperplasia** of the breast
  - Personal history of **ovarian cancer**
  - History of uterine **fibroids**, endometriosis
  - Active **gallbladder** disease (cholangitis, cholecystitis)
  - Chronic liver disease, severe **hypertriglyceridemia**
Non-hormonal treatments for menopausal symptoms

- **Lifestyle interventions:**
  - Sleeping in a cool room,
  - Watching intake of caffeine, alcohol and hot, spicy foods

- **Vaginal dryness may be treatable with topical estrogen**

- **Botanicals (no clear consistent evidence that they are effective and inconsistent preparations):**
  - Black Cohosh appears to be safe when used for <6 months.
  - Phytoestrogens (isoflavones) are produced by plants such as soy, wild yam; most studies did not show a benefit.
  - Dong quai root (women taking warfarin should avoid it)
  - Kava (may be dangerous to the liver)
  - Ginseng may help improve well-being, moodiness, and sleep.
  - Valerian may help with sleep disturbances.

Non-hormonal treatments for menopausal symptoms

- Non-botanical supplements
  - Vitamin E may have a modest effect in relieving hot flashes in some women.
  - Melatonin may help in falling asleep and staying asleep.
- Mind/body therapies—useful in relieving hot flashes or the emotional symptoms of menopause.
  - Yoga, focused breathing, mindful meditation, acupuncture, aromatherapy, massage
- In women with contraindications to HRT, if lifestyle changes do not provide enough relief:
  - Gabapentin 300-2400mg/day,
  - selective serotonin reuptake inhibitor (SSRI; Paroxetine 10-20 mg/day, Fluoxetine 20mg/day),
  - serotonin norepinephrine reuptake inhibitor (SNRI; Venlafaxine 75-150 mg/day) to improve sleep,
  - clonidine, bellargal etc.
Conclusions

• HRT/MHT is a mixed picture of benefits and risks. It has a net beneficial effect for some women and a net harmful effect for others

• It is important to be open-minded

• Cost effective

• It is the most effective treatment for vasomotor s/s

• Benefit-to-risk ratio strongly influenced by:
  • a woman’s age,
  • time since menopause onset,
  • underlying risk factor profile

• Transdermal estrogen therapy has been associated with lower risks of blood clots and strokes
Conclusions

- Decision making must be individualized
- Discuss a woman’s quality of life priorities and her personal risk factors
- Difference in balance of benefits & risks when HRT is used for short-term symptom management vs long-term disease prevention.
- Long-term use of HRT/MHT for prevention of chronic diseases in women ≥65 years of age is no longer recommended
- Make reasonable Rx decisions based on evidence rather than emotional decisions based on fear
References


- Postmenopausal hormone therapy: an Endocrine Society scientific statement. J Clin Endocrinol Metab. 2010;95(7 Suppl 1):s1-s66


- [http://www.hormone.org/menopausemap](http://www.hormone.org/menopausemap) (resource for women)
Thank you
Androgen production and therapy in women

In premenopausal women, androgens are produced in the adrenal gland, the ovary, and from the peripheral conversion of pro-hormones. The major androgens are:

- Dehydroepiandrosterone sulfate (pro-hormone) ~100% by the adrenal gland
- Dehydroepiandrosterone (DHEA, pro-hormone) adrenal gland (50%), ovary (20%), and peripheral conversion of DHEA-S (30%)
- Androstenedione (pro-hormone) adrenal gland (50%) and the ovary (50%)
- Testosterone by adrenal gland (25%), the ovary (25%), and from the peripheral conversion of androstenedione (50%). Daily production rate is ~0.1 - 0.4 mg/day (compared with 5 -7 mg/day in men,) and circulating levels are between 20-70 ng/dL. Lowest concentrations found during the early follicular phase.
- Dihydrotestosterone (DHT) by 5α reduction of testosterone
- Serum androgen concentrations gradually decline in women of reproductive age, with no further decrease after clinical menopause (since it is produced by the postmenopausal ovary under influence of elevated gonadotrophins)
Role of androgens in females

- Precursors for estrogen synthesis
- Important regulator of normal follicle maturation
- Play a role in female sexual function (?)
- Possible beneficial effects on bone health
- May adversely affect the risk of cardiovascular disease

Androgen deficiency syndromes can occur in:
- Bilateral oophorectomy
- Primary adrenal insufficiency
- Hypopituitarism, particularly women with both ACTH and gonadotropin deficiency
- Anorexia nervosa
- Medications including oral contraceptives, oral estrogens (menopausal replacement) reduce serum free testosterone concentrations by increasing serum SHBG; glucocorticoids->adrenal androgen suppression
Androgen therapy in women

• Testosterone therapy has been shown to improve female sexual function in carefully selected populations.
  • Transdermal testosterone (Intrinsa 300 ug patch) applied twice weekly (not available in U.S.),
  • topical compounded 1% testosterone cream (0.5 grams daily)
  • gels would need to be applied in approximately 1/10th the male prescribed dose.
  • Estratest (methyltestosterone + estrogen) was taken off the U.S market in 2009.
  • DHEA replacement OTC 25-50 mg/d appears to be effective for improving sense of well-being in women with adrenal androgen deficiency (eg primary adrenal insufficiency, hypopituitarism->ACTH deficiency, chronic glucocorticoid use)

• Side effects include acne and hirsutism (both were dose- and duration-related and generally reversible); HDL-C can decrease; Testosterone is metabolized to estrogen->abnormal uterine bleeding or breast symptoms.
Vasomotor and vulvo-vaginal atrophy symptoms

- HRT is the most effective treatment for healthy women
  - For vasomotor symptoms,
  - diminished sleep quality,
  - difficulty concentrating,
  - symptoms of vulvovaginal atrophy
  - reduced QOL.
- ~50% chance of recurring symptoms after HRT is stopped
- Local ERT may benefit some women with dryness, dyspareunia, overactive bladder.
  - Can use 0.5 grams of cream or 10-25 ug of the vaginal pill twice a week
  - Ospemifene (Osphena, SERM) 60mg PO/day
Risk factors for breast cancer

- Being a woman is the main risk for breast cancer (F>M 100 times)
- 2 of 3 women with invasive breast cancer are 55 or older
- ~5-10% of breast cancers are thought to be linked to inherited changes, most commonly BRCA1 and BRCA2 genes. Women with these gene changes have up to an 80% chance of getting breast cancer during their lifetimes
- over 85% women who get breast cancer do not have a family history of this disease, so not having a relative with breast cancer doesn’t mean you won’t get it
- Breast cancer risk is higher among women whose close blood relatives (from either the mother’s or father’s side) have this disease.
- A woman with cancer in one breast has a greater chance of getting a new cancer in the other breast
- White females > AAF (in <45yr age AAF > WF); Asian, Hispanic, and Native-American women have a lower risk of getting and dying from breast cancer
- Women with denser breast tissue have a higher risk
Breast cancer

- Increased risk of breast cancer with HRT may be due to promotion of preexisting cancers that are otherwise too small to be diagnosed by imaging or clinically.
- Incidence of breast cancer decreased by 6.7% in 2003. This was thought to be due to many women discontinuing HRT after WHI results in 2002 (but also due to changes in other risk factors; too early to decre within 1 year).
- Breast cancer prognosis is not influenced by high hormone levels during pregnancy, and oral contraceptive use has not been consistently shown to increase breast cancer risk.
- Use of postmenopausal hormone therapy after breast cancer remains controversial. Choice of hormone regimen (E2 & P) may modify the risk for recurrence.
- A woman with a first-degree relative (mother, sister, or daughter) who had premenopausal breast cancer is at increased risk by virtue of family history, her risk of breast cancer is not thought to be increased further by HRT use.
HRT in patients with h/o or risk for breast cancer

- Although there are many observational studies of breast cancer patient follow-up, there are no published consensus statements or guidelines regarding appropriate medical follow-up after mastectomy.
- Management of ovarian cancer risk in *BRCA* mutation carriers who have undergone prophylactic mastectomy: prophylactic b/l salpingoopherectomy (PBSO) is recommended.
- Due to the reduction in breast and ovarian cancer risk associated with the removal of the ovaries, women with *BRCA* gene mutations can elect to undergo PBSO without undergoing prophylactic mastectomy (PBSO is associated with a 46-56% breast cancer risk reduction).
- Some experts advocate the removal of the uterus because women with *BRCA* mutations may eventually take tamoxifen, which is associated with an increased risk for endometrial carcinoma, also if hysterectomy is done at the time of PBSO, unopposed estrogen could be used as HRT if needed, with negligible breast cancer risk.
- Preventive b/l mastectomy may significantly reduce (by about 90%) the chance of developing breast cancer in moderate- and high-risk women (eg 1st degree relative w/ early breast Ca, BRCA+).

Coronary heart disease (CHD)

- Premenopausal women have a lower incidence of CHD than men but they lose this benefit after menopause, likely due to endothelial dysfunction.
- ERT may reduce CHD risk when started in younger & more recently menopausal women without a uterus by slowing the development of calcified atherosclerotic plaque.
- Women who initiate HRT less than 10 years after menopause tend to have a lower risk for CHD but those who initiate more than 10 years after menopause can be at increased risk for CHD.
- HRT should not be recommended for prevention of heart disease.
Stroke (CVA)

- HRT in younger women (ages 50-59 y) at study entry, who are at lower absolute risk of stroke, had no significant effect on carotid IMT or risk of stroke.
- In older women, the increased risk is of ischemic stroke and no effect on the risk of hemorrhagic stroke.
- A strong relationship between dose of oral conjugated estrogen and stroke was found in some studies ie higher the E2 dose, greater the risk.
Venous thromboembolism (VTE)

- VTE risk emerges soon after HRT initiation (i.e., during the first 1-2 years)
- The relative risk is high but absolute risk is small, the excess risk seems to decrease somewhat in time.
- Women with a previous history of VTE, obese women, smokers or women who possess a factor V Leiden mutation are at increased risk of VTE with HT use.
- Limited observational data suggest lower risks of VTE with transdermal than with oral ET but there are no large comparative RCT data.
Ovarian & endometrial cancer

- Unopposed estrogen can cause endometrial hyperplasia and a 2-3 fold increase in the risk of endometrial cancer in a woman with a uterus.
- Addition of progestogen reduces this risk to lower levels than those seen in women not on HRT.
- In general, HRT is not recommended in women with a history of endometrial cancer. Progestogen alone could be considered for the management of vasomotor symptoms but no long-term data are available.
- Observational data & 1 meta analysis suggest a possible weak association of ovarian cancer with long term (at least 10 years) HRT, but data are inconclusive since the prevalence is low.
- In the WHI, HRT was not associated with a statistically significant increase in ovarian cancer after a mean of 5.6 years of use.
- Women at increased risk of ovarian cancer (eg, those with a family history or a BRCA mutation) should be counseled about this potential association.
Cognitive function and dementia

- Estrogen increases levels of choline O-acetyl-transferase in the brain, the enzyme needed to synthesize acetylcholine, a neurotransmitter thought to be critical for:
  - memory;
  - may enhance short- and long-term memory;
  - protects neurons from oxidative stress,
  - increases glucose transport and cerebral blood flow,
  - stimulates the branching of neurites.

- A small study of 117 women found that in the 1st year after menopause, they performed worse on measures of verbal learning and memory and fine-motor skills, compared to women in the late reproductive and late transition stages.*

- For postmenopausal women older than 65 years,
  - HRT does not improve memory or other cognitive abilities. Estrogen alone appears to be neutral in women over 65.

- Available data do not adequately address whether HRT used soon after menopause increases or decreases the rate of cognitive decline or later dementia risk.

Troubleshooting

**Bleeding/breast tenderness:**
- Consider lowering E2 dose, or increase progesterone in increments until bleeding stops/ADRs occur (bloating/fluid retention/mood swings)
- Switch to cyclic regime (continuous regimes work better ≥5yrs post menopause)
- Transvaginal ultrasound, if endometrial stripe >5mm
  -> endometrial Bx
- Consider SERM or other alternatives

**Moodiness, bloating:**
- Change/lower dose of progestin

**Hot flashes persist:**
- Measure E2. If >150pg/ml => rule out other causes.
- Otherwise can try higher E2 dose

**Patient has hot flashes but still has periods:**
- Low dose BCP if no contraindication, eg alesse-28, loestrin 1/28
- Low dose E2 alone (her own progest can cause periods)
Normal menstrual cycle
Women’s Heath Initiative 2002

- Randomized, double-blinded placebo-controlled trials-intended as test of primary prevention in women ages 50-79, planned for 8.5 years
- •Estrogen + Progestin (uterus intact); stopped at 5.2 years
  - PremPro® 0.625 CEE/2.5 MPA daily; n=8506
  - Placebo; n=8102
- •Estrogen alone (hysterectomized); stopped at 6.8 years
  - Premarin® 0.625 CEE daily; n=5310
  - Placebo; n=5429
- •Endpoints
  - Cardiovascular events (new heart attack, cardiac death)
  - Other clinical events (fractures, cancers, VTE, stroke)
- •Mean age 63
- •BMI 28.5 kg/m 2
- •Never User 74%, Past User 20%, Current User 6%
Symptoms of menopause

- Long periods of unopposed estrogen exposure -> anovulatory bleeding and endometrial hyperplasia.
- Hot flashes- Due to thermoregulatory dysfunction, initiated at the level of the hypothalamus by estrogen withdrawal. Self limited, usually resolve without treatment within 1-5 years, ~9% women continue to have hot flashes until after age 70.
- Sweating & palpitations
- Sleep disturbances
- Vulvovaginal dryness, itching, dyspareunia, lack of sexual desire.
- Atrophic urethritis, stress and urge urinary incontinence, recurrent UTI’s
- Depression, labile mood, impaired memory & concentration
- Menstrual migraines
- Wrinkling of skin, dry skin
- Thinning of scalp hair, hirsutism
- Fatigue, diffuse joint pains, myalgias
- Impaired balance
- Bone loss
- Increased CHD?

Yet, 7 out of 10 women suffering from menopausal symptoms are not treated. 6 out of 10 are not discussing treatment options with their doctor. ~50% of all women (and their physicians) have a negative impression of HRT.
# Transition to menopause

<table>
<thead>
<tr>
<th></th>
<th><strong>Perimenopause</strong></th>
<th><strong>Menopause</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>~4 yrs before the final menstrual period, can last for several years</td>
<td>occurs at a mean age of 51 yrs in U.S. women (5% &gt;55 yrs, 5% between 40-45 yrs)</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>some menstrual irregularity</td>
<td>12 months amenorrhea</td>
</tr>
<tr>
<td></td>
<td>Cycle length &gt;7 days diff from normal-&gt; &gt;2 skipped cycles</td>
<td></td>
</tr>
<tr>
<td><strong>Follicular number</strong></td>
<td>decreases</td>
<td>Marked decline due to progressive atresia</td>
</tr>
<tr>
<td><strong>Inhibin B</strong></td>
<td>falls due to decr follicles</td>
<td></td>
</tr>
<tr>
<td><strong>AMH</strong></td>
<td>falls</td>
<td></td>
</tr>
<tr>
<td><strong>Serum FSH</strong></td>
<td>begins to rise (&gt;25 mIU/ml)</td>
<td>high</td>
</tr>
<tr>
<td><strong>Estradiol secretion</strong></td>
<td>relative preservation due to incr aromatase activity</td>
<td>low</td>
</tr>
</tbody>
</table>

Early postmenopause=1st 5 years after final menstrual period
Late postmenopause= from 5 yrs till end of life
Inhibin B=probably the earliest easily measurable marker of follicular decline.
AMH=antimüllerian hormone, another product of the granulosa cell
# Effects of HRT other than menopausal symptoms

<table>
<thead>
<tr>
<th>Risk</th>
<th>oral E2 + P</th>
<th>transdermal E2</th>
<th>any E2</th>
<th>E2 only</th>
<th>Tibolone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>sl incr</td>
<td>sl incr</td>
<td>no effect</td>
<td>sl decr</td>
<td>no effect</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>decr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT/PE</td>
<td>2x incr</td>
<td>no incr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td>no effect</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10yr menopausal</td>
<td>no incr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;10yr menopausal</td>
<td>incr</td>
<td></td>
<td></td>
<td>no incr/?decr</td>
<td></td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;60yr age</td>
<td>small incr</td>
<td>no incr at &lt;50ug</td>
<td>small incr</td>
<td>small incr</td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td>incr if started</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;65yr age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

E2=estrogen, P=progesterone

*< 2yr since last period->sequential with prometrium 200mg/d for 12 days/month
> 2yr since last period->continuous combined with prometrium 100mg/d with transdermal E2

# Examples of FDA approved bioidentical HRT

<table>
<thead>
<tr>
<th>Hormone</th>
<th>route</th>
<th>brand</th>
<th>dose</th>
<th>freq</th>
</tr>
</thead>
<tbody>
<tr>
<td>17β estradiol</td>
<td>PO</td>
<td>estrace</td>
<td>0.5, 1, 2, 0 mg/d</td>
<td>daily</td>
</tr>
<tr>
<td></td>
<td>transdermal</td>
<td>climara</td>
<td>0.025, 0.375, 0.05, 0.075, 0.1 mg/d</td>
<td>once weekly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>fempatch</td>
<td>0.025 mg/d</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>menostar</td>
<td>0.014 mg/d</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>alora</td>
<td>0.025, 0.05, 0.075, 0.1 mg/d</td>
<td>twice weekly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>esclim</td>
<td>0.025, 0.375, 0.05, 0.075, 0.1 mg/d</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>vivelle</td>
<td>0.025, 0.375, 0.05, 0.075, 0.1 mg/d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>transdermal gel</td>
<td>divigel</td>
<td>0.1%, 0.003, 0.009, 0.027 mg/d</td>
<td>daily</td>
</tr>
<tr>
<td></td>
<td>vaginal cream</td>
<td>estraderm</td>
<td>0.05, 0.1 mg/d</td>
<td>twice weekly</td>
</tr>
<tr>
<td></td>
<td>vaginal ring</td>
<td>estrace</td>
<td>2-4 gm/d</td>
<td>for 1-2 weeks then 1 gm/d</td>
</tr>
<tr>
<td>Estradiol acetate</td>
<td>PO</td>
<td>femtrace</td>
<td>0.45, 0.9, 1.8 mg/d</td>
<td>daily</td>
</tr>
<tr>
<td></td>
<td>vaginal ring</td>
<td>femring</td>
<td>0.05, 0.1 mg/d</td>
<td>continuous</td>
</tr>
<tr>
<td>Estradiol hemihydrate</td>
<td>vaginal tablet</td>
<td>vagifem</td>
<td>0.01 mg/d</td>
<td>1 tab/d x 2wks, then 1 tab twice a week</td>
</tr>
<tr>
<td>Estropipate</td>
<td>PO</td>
<td>ortho-est</td>
<td>0.625, 1.25, 2.5, 5.0 mg/d</td>
<td>daily</td>
</tr>
<tr>
<td>Progesterone</td>
<td>PO</td>
<td>prometrium</td>
<td>100, 200 mg/d</td>
<td>continuous or cyclical</td>
</tr>
</tbody>
</table>
Bioidentical hormone replacement therapy

- Synthesized by chemically extracting diosgenin from plants (yams, soy) -> chemically modified to produce precursor progesterones -> used to synthesize bioidentical estrogens & androgens.

- Refers to the use of hormones that are chemically identical to those produced in a woman's body - though they are also associated with the practices of pharmaceutical compounding and saliva testing to determine, and adjust a woman's hormone levels.

- Non bioidentical estrogen includes conjugated equine estrogens (extracted from urine of pregnant mares), ethinyl estradiol (15-20x more active than oral estradiol)
Tibolone

- Widely used in Europe and other countries for nearly 20 years (but is not available in the US).
- A synthetic steroid whose metabolites have estrogenic, androgenic, and progestogenic properties.
- It reduces vasomotor symptoms when compared to placebo, and has a beneficial effect on bone mineral density. Limited data suggest that it may also have a modest effect for symptoms of sexual dysfunction.
- It has been associated with an increased risk of stroke, and therefore, it is not recommend for routine use for management of menopausal symptoms in the U.S.
Conclusions

- The benefits of MHT outweigh the risks for the treatment of symptoms associated with menopause if prescribed before the age of 60 years or within 10 years after menopause.
- MHT may prevent osteoporosis-related fractures in at-risk women before the age of 60 years or within 10 years after menopause.
- Review of randomized clinical trials and observational data shows that MHT using standard-dose monotherapy with estrogen may decrease coronary heart disease and all-cause mortality in women <60 years and within 10 years of menopause.
- Oral MHT increases the risk for venous thromboembolism and ischemic stroke, but the absolute risk is rare in women <60 years.
- Increased risk for breast cancer may be a concern with combination MHT using estrogen and progesterone and may be related to duration of use. The risk is small and decreases after treatment is discontinued.
- Use of custom-compounded bioidentical hormone therapy is not recommended.
- MHT should not be used in women who have a history of breast cancer.
Conclusions & recommendations*

- Hormone therapy is the most effective treatment for menopausal symptoms such as hot flashes. It is currently recommended for short-term (≤5 yrs) management of moderate-to-severe vasomotor flushes.
- Younger women (under 60 yrs) who have recently started menopause are at a lower risk for ADR’s than older women when taking low doses of hormone therapy.
- Women who still have a uterus need to take a progestogen along with the estrogen to prevent cancer of the uterus.
- Women who have had their uterus removed can take estrogen alone. Because of the apparent greater safety of estrogen alone, there may be more flexibility in how long women can safely use estrogen therapy.
- If women have only vaginal dryness or dyspareunia (discomfort with intercourse), the preferred treatments are low doses of vaginal estrogen or Osphena (ospemifene, a selective estrogen receptor modulator).

*Statement of agreement 2012 from The North American Menopause Society, American Society for Reproductive Medicine, The Endocrine Society, AACE.
Conclusions & recommendations (contd)

- Both ERT and E2+P therapy increase the risk of blood clots in the legs and lungs, similar to birth control pills, patches, and rings. Although the risks of blood clots and strokes increase with either type of HRT, the risk is rare in the 50-59 year old age group.

- Transdermal estrogen therapy (patches, gels, and sprays) and low-dose estrogen pills approved by the FDA have been associated with lower risks of blood clots and strokes than standard doses of estrogen pills, but RCTs data directly comparing oral and transdermal hormone therapy is not yet available.

- An increased risk of breast cancer is seen with ≥5 years of continuous estrogen/progestogen therapy. The risk decreases after HRT is stopped. Use of E2 alone for an average of 7 years in the Women’s Health Initiative trial did not increase the risk of breast cancer. However, there is a lack of safety data in breast cancer survivors.
Conclusions & recommendations (contd)

- E₂+P and E₂ alone decreased risk for fractures but increased risk for stroke, thromboembolic events, gallbladder disease, and urinary incontinence.
- E₂+P increased risk for breast cancer and probable dementia, whereas estrogen alone decreased risk for breast cancer.
- Consideration should be given to the woman’s quality of life priorities, her personal risk factors such as age, time since menopause, her risk of blood clots, heart disease, stroke, and breast cancer.
- Long-term use of E₂+P or E₂ alone for prevention of disease (eg prevention of CHD, treatment of osteoporosis and prevention of dementia or cognitive decline in women ≥65 years of age) is no longer recommended.
ELITE: Early Versus Late Intervention Trial With Estradiol

- Postmenopausal <6 years, or ≥ 10 years
- hypothesis
  - 17B-estradiol (estrogen) will reduce the progression of early atherosclerosis if initiated soon after menopause when the vascular endothelium (lining of blood vessels) is relatively healthy, versus later when the endothelium has lost its responsiveness to estrogen.
  - 17B-estradiol (estrogen) will reduce the progression of cognitive decline if initiated soon after menopause when healthy brain tissue remains responsive to estrogen, versus later when brain tissue has lost its responsiveness to estrogen.

Estimated Study Completion Date: July 2013