Menopause and Hormone Replacement Therapy

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London, UK
May 6, 2017
Why so much Confusion?
The Importance of passing on your memes: Your “infectious ideas”
What Are “Normal” Ooestrogen Levels?

Life Cycles of Estrogen and Testosterone
What Are “Normal” Oestradiol Levels

- Follicular phase [20-40pg/mL]
- Luteal phase [60-80pg/mL day 21]
- Perimenopause [all over the map]
- Menopause early [15-25pg/mL]
- Menopause late [5-15pg/mL]
Age vs Oestradiol levels (pmol/L)

- Columbia, US
- Guernsey, UK
- Nurses' HS
- NYU, US
- Ordet, Italy
- Rancho Bern
- RERF, Japan
- SOF, US
- Wash Co, US
- Rancho sub

10pg/mL
Unopposed estradiol patch at 0.014mg/day vs placebo raised estradiol levels from 4.8 to 8.5pg/mL at one year and improved BMD in spine and hip when used in combination with Calcium and Vitamin D supplementation. (One women developed endometrial hyperplasia in the estradiol group)
Oestrogen-only Rx
Do you have to remove the uterus to give oestrogen only?

The Female Patient Supp, February 2004, pg 19
Overall risk and benefit are profoundly affected by age of initiation of therapy.

CHD: Coronary heart disease; VTE: Venous thromboembolism; WHI: Women's Health Initiative.

Data taken from.\textsuperscript{[18,25,26]}
Pre-diagnosis oophorectomy, estrogen therapy and mortality in a cohort of women diagnosed with breast cancer

Hazel B Nichols, Amy Trentham-Dietz, Polly A Newcomb, Kathleen M Egan, Linda J Titus, John M Hampton, and Kala Visvanathan

Abstract

Introduction

Pre-diagnosis oophorectomy and estrogen therapy could impact mortality due to breast cancer and cardiovascular disease (CVD) among breast cancer survivors. Elective bilateral oophorectomy at the time of hysterectomy for benign conditions is not uncommon among US women.

Methods
B. Breast Cancer Mortality

Cumulative Mortality

Years since breast cancer diagnosis

- No surgery, no estrogen
- TAHBSO, no estrogen
- TAHBSO, estrogen

Log rank p=0.003
C. Cardiovascular Disease Mortality

![Graph showing Cardiovascular Disease Mortality over Years since Breast Cancer Diagnosis]

- **No surgery, no estrogen**
- **TAHBSO, no estrogen**
- **TAHBSO, estrogen**

Log rank $p < 0.001$
A. All-Cause Mortality

Cumulative Mortality

Years since breast cancer diagnosis

- No surgery, no estrogen
- TAHBSO, no estrogen
- TAHBSO, estrogen

Log rank p<0.001
Balanced Signaling
The Effect of Hormones on Aging

- What do hormones do as we leave the reproductive period
  - They protect brain, blood vessels, and bones
  - They provide a buffer for adrenal stresses
  - They delay aging in rapidly turning over epithelium (skin, gut)
Effect of Age on HRT

- Because of decreasing ability to metabolise drugs with age hormone doses should be adjusted after 65.
- In one study of MPA and oestradiol valerate the area under the curve averaged 1.6-1.8 times higher in those over 65 vs under 60.
- If attempting to mimic normal hormone levels after menopause, levels must be adjusted after 65 as well.
Estradiol is probably hormentic...too much or too little is a bad thing.
The things that make oestrogen good for the brain make it bad for the breast!
My HRT Rules

- Normal menopause is not a deficiency state
- Surgical menopause *is* a deficiency state
- Goal is to maintain maximum flexibility of the system
- Use the Matrix before you use the drugs
Hormones are to trick your body into thinking you are still young.

Mimic premenopausal hormone levels and fluctuations

Replace to follicular phase premenopausal levels with continuous combined hormones

Replace to normal menopausal levels

Any addition of hormones increases risk of breast cancer and thrombosis

More hormones

Lowest amount, shortest time

Less hormones

No

I AM HERE! Where are you?
Cellular Stress

ROS
O₂ Consumption
ATP Synthesis
Calcium Regulation
Fusion/fission

Fatigue, decreased steroid production
<table>
<thead>
<tr>
<th>Phase</th>
<th>Duration</th>
<th>Cycles</th>
<th>Flow</th>
<th>Symptoms</th>
<th>Flashes</th>
<th>Hormones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase A</td>
<td>2-6 mo</td>
<td>Regular, ovulatory shorter cycles, short follicular phases</td>
<td>Increased or the same</td>
<td>↑PMS, ↑Dysmenorrhea, breast symptoms, exacerbation of headaches and migraines</td>
<td>First onset, cyclic before flow or midcycle (very often in the early morning)</td>
<td>Normal FSH, ↑E₂ short follicular phases, LH normal, ? inhibin low</td>
</tr>
<tr>
<td>Phase B</td>
<td>2-6mo</td>
<td>Regular, often ovulatory disturbances</td>
<td>Increased</td>
<td>↑↑PMS, intermittent dysmenorrhea</td>
<td>Cyclic still during or at the end of sleep</td>
<td>↑↑FSH intermittent, ↑E₂ at flow for some nonovulatory cycles, LH normal, ? inhibin low</td>
</tr>
<tr>
<td>Phase C</td>
<td>1-2yr</td>
<td>Irregular, alternate short and long cycles, ovulation less than 50%</td>
<td>↑↑ or less, often alternating</td>
<td>Less PMS but erratic, menstrual-type cramps may occur any time</td>
<td>Still cyclic, but less predictable, onset in daytime</td>
<td>Normal alternating with high E₂, ↑FSH persistently, ↑ LH occasionally, ? inhibin low</td>
</tr>
<tr>
<td>Phase D</td>
<td>1-2yr</td>
<td>Oligoamenorrhea, rare ovulation</td>
<td>Spotting alternating with flooding</td>
<td>No predictable symptoms, menstrual-like cramps in a few women, anytime</td>
<td>Erratic, more persistent in long cycles</td>
<td>↑↑FSH, ↑LH, E₂ normal except intermittent prolonged high levels, inhibin low</td>
</tr>
<tr>
<td>Phase E</td>
<td>1yr</td>
<td>Amenorrhea</td>
<td>None</td>
<td>Few or confusing without subsequent flow</td>
<td>May become consistent daily, or decrease</td>
<td>↑↑LH Normal or low E₂, but intermittent low or high levels, below assay inhibin sensitivity</td>
</tr>
</tbody>
</table>

Prior JC: Endocrine Reviews 1998;19 (4): 397-428
HT or HRT?
Who needs hormone (replacement) therapy?

Consider:

- Oophorectomy
- Hysterectomy & Tubal Ligation
- Autoimmune oophoritis
- Premature ovarian failure
- Hot flashes
Oophorectomy

There is no other endocrine organ that is as casually removed and as unlikely to have its missing hormone/hormones replaced as the ovary.
Ovaries don’t DO anything after menopause.

Don’t menopausal hormones come from the periphery?
Ovarian Hormone Contribution after Menopause

<table>
<thead>
<tr>
<th></th>
<th>Ovarian</th>
<th>Peripheral</th>
<th>Fold difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testost.</td>
<td>7.2 (0.2–62.0)</td>
<td>0.3 (0.2–0.8)</td>
<td>24</td>
</tr>
<tr>
<td>Andros</td>
<td>4.3 (0.0–21.7)</td>
<td>1.1 (0.6–1.6)</td>
<td>4</td>
</tr>
<tr>
<td>DHEA</td>
<td>8.8 (3.6–33.8)</td>
<td>5.2 (2.0–9.0)</td>
<td>2</td>
</tr>
<tr>
<td>E1</td>
<td>150 (24–1276)</td>
<td>50 (24–88)</td>
<td>3</td>
</tr>
<tr>
<td>E2</td>
<td>99 (5–834)</td>
<td>15 (4–32)</td>
<td>7</td>
</tr>
</tbody>
</table>

Risks of Oophorectomy

- Increased carotid intima-media thickness.\(^1\)
- Increased risk of death from coronary artery disease (CAD).\(^1,2\)
- Decreased bone density, increased risk of osteoporosis and hip fracture.\(^1,2\)
- Increased risk of cognitive impairment, Parkinson’s, depression, and anxiety.\(^3,4,5\)
Effect of Oophorectomy

- Increased death from all causes.\(^1\)

- Increased risk of all cancers except ovarian cancer.\(^2,3\)
What if the ovaries are still present but not functioning well?
Damage to Ovarian Blood Supply

Hysterectomy and Tubal Ligation
Hysterectomy

Are ovaries left behind functioning normally?
Testosterone Levels Following Hysterectomy +/- Oophorectomy

Post Tubal Ligation Syndrome

- Debated as to whether it exists.

- Bilateral Tubal Ligation has been shown to have an effect on ovarian blood supply and function.\(^1,^2\)

- Although menstrual periods did not change significantly, salivary progesterone levels declined.\(^3\)
Autoimmune Oophoritis
The ovary is commonly the target of an autoimmune attack leading to the ovarian dysfunction which can be manifested as premature ovarian failure (POF), polycystic ovary syndrome (PCOS), unexplained infertility as well as endometriosis.
Premature Ovarian Failure (POF) is caused by autoimmunity, toxins, drugs, or genetic defects.

Incidence:

1:10,000 by age 20
1:1000 by age 30
1:100 by age 40

The majority of women seeking HRT are having hot flashes and brain symptoms
Hot flashes are no laughing matter
Danger of Hot Flashes:

- Hot flashes are associated with higher carotid intima-media thickness and lower BMD.\(^1\)
- Hot flashes are associated with lower HDL and ApoA1 and higher ICAM-1 (intracellular adhesion molecule-1) suggesting higher vascular risks.\(^2\)
- Hot flashes are associated with a higher risk of depression.\(^3\)
It is important to remember that hot flashes do not always correlate with oestrogen levels…

So while addressing hot flashes is important, oestrogen is not always the correct treatment!
Who needs treatment

- Women without ovaries
- Women with autoimmune destruction of ovaries
- Women who need help NOW!
- Women who are willing to take the risk
Where to Measure?

- **SERUM** — circulating hormones, both bound & un-bound

- **SALIVA** — unbound, free, active hormone. Hormone levels are extremely low and therefore difficult to measure and steroid hormone appear to be secreted

- **URINE** — combination of both the endocrine production and peripheral production of conjugated hormones & metabolites *(some hormone levels have to be evaluated by looking at their metabolites)*

- **TISSUE** - wishful thinking or does saliva or capillary approximate this?
Where to Measure?

THUS, the choice of sample type is determined by:

- the physiology of the specific hormone,
- the clinical question being asked, AND
- the therapeutic modalities being used
“Blood is a fluid connective tissue that interacts with all other human tissues, and peripheral blood cells have been found to reflect system wide biology.”

Oestrogen metabolites

- Estrone-Sulfate
- Estrone
- Estradiol
- 16α-Hydroxy-estrone
- 2-Hydroxy-estrone
- 4-Hydroxy-estrone
- Estriol
- 2-Methoxy-estrone
- 4-Methoxy-estrone
Salivary Testing
Problems with Salivary hormone testing

- Some hormones are metabolized in the gland.⁶

- Hormone levels in saliva are much lower than serum (1 to 5%, which in menopause are already very low, blood level 20-30pg/ml in serum = 0.4-.0.6 pg/ml in saliva and requires technically more challenging assays).³

- Rapid fluctuations in levels.¹ May necessitate multiple samples for accuracy.
The Progesterone Conundrum

- When measuring *endogenous* progesterone, saliva appears to be a reliable reflection of blood levels.

- Following progesterone cream or gel dosing, extraordinarily high levels of progesterone are seen in saliva and in capillary beds.
Does salivary progesterone reflect tissue levels?

The ultimate question becomes:
Why are hormone levels in the salivary gland so high
but in the endometrial cell insufficient to produce
secretory effects?

And if endometrial delivery is low, how much is
transferred to the breast or the brain (both high-fat
organs), and why are there better effects on the
brain with oral than with transdermal administration?

*These issues make salivary testing difficult and results problematic*
Urinary Testing
Quick Review:
Metabolism (degradation) of oestrogens

- Phase I
  - Hydroxylation in the 2OH, 4OH, 16OH positions

- Phase II
  - Glucuronidation
  - Sulfation
  - Methylation
24 Hour Urine –
What does it tell you?

- Total amount of hormone contributed by both endocrine and peripheral production - total amount of hormones bound and unbound minus what is excreted in bowel.

- How your body is using a hormone (to some extent what pathways are “turned on”).

- Reflects unbound fraction (of original hormone) however some hormones (like progesterone) are only seen as metabolites.
Total Metabolites of oestrogen in Tissue and Urine

Key Points in Urine Testing

- These are **metabolites** and oral hormones produce high results and will not reflect tissue levels.
- Collection problems are an issue.
- Kidney function affects results.
- GI excretion is not covered.
- Relationship to tissue levels uncertain.
Dried urine spot (DUS) tests: Metabolites

- **Recent rise in popularity of urine spot tests**
  - Gold standard is still 24-hour urine, but 24-hour collections are inconvenient and it is not uncommon for patients to make collection and reporting mistakes, such as missed samples and errors in measuring total urine volume which can affect results.

- **Cons of dried urine spot tests:**
  - Inaccuracy in doing a random spot due to analyte variability during the day
  - **Minimal support in literature to date**
Dried urine spot (DUS) tests: Metabolites

Pros:

- Simple to collect (no jugs or refrigeration), specimen stability

- One lab: “Urine dried on filter paper produces results nearly identical to liquid urine while improving on sample transport, size and stability.”

- “Creatinine can also be measured in dried urine, providing a way to normalize results by using a correction factor taking into account hydration status.”


Things to remember about hormone testing:

1. Compare like samples and same technology only
2. Remember tissue level is what you really want to know
3. Use mainly to prevent overdosing hormones
Why I measure hormones in blood:

- Compartment closest to breast-presumably equilibrates to some degree.
- I can evaluate, treat, and re-evaluate using the same medium and without waiting as long before retesting after dosage adjustment.
- There is more data in the literature to tell me what normal is.
SHBG: A functional test of hormone effect?

- When testosterone levels are within normal range, SHBG reflects total oestrogen load going through the liver.

- I use it as a “functional” test of oestrogen levels (total) in the body.

Recall that SHBG has a much higher affinity for androgens than oestrogens.
Why I measure (some) hormones in urine

- Can measures total production/metabolism per day (24 hour urine collection)—learn more about what enzymes are turned on or off.

- I can measure 2 and 4 methoxy-oestrogens.

- Fluctuations over 24 hours can be evened out (good or bad).

Problems:

- End products are measured. Relevant hormones may not correlate with blood depending upon metabolic pathways such as gut metabolism and excretion.

- Expense when added to blood testing.
Whatever you use …

- **Become familiar** with the test.

- **Test hormone levels** following therapy and regularly if possible. **Retest** for dose adjustments at 60-65 years of age.

- **Combine laboratory and clinical information** to make your decisions about HRT.
Now we are ready to discuss treatment:
What hormones should you use?

Bioidentical
What is bio-identical hormone therapy

Identical…well almost!
Current thinking:

- The Endocrine Society has defined bio-identical hormones as “compounds that have exactly the same chemical and molecular structure as hormones that are produced in the human body.”
Current thinking:

- **NAMS: Bioidentical** hormones do not have to be custom-compounded (meaning custom mixed). There are many well-tested, **FDA-approved hormone therapy** products that meet this definition and are commercially available from retail pharmacies (in USA).
Problems with approved products

- Oestradiol comes in patches that can be cut to titrate dose but levels are constant through 24 hours and wax and wain over the course of the patch life.

- Progesterone is only available in oral which is in peanut oil and vaginal (cream and ovule) which is expensive and only approved for infertility\(^1\).

- Testosterone is only FDA approved for women as methyltestosterone.
What about compounded hormones
When is CBHT O.K.?

“According to the FDA and NAMS, use of CBHT is justified when a woman cannot tolerate some of the ingredients in an approved product (peanut allergy), when she needs a lower dose than is available, or she has specific medical needs (?high SHBG?)” Testosterone was never mentioned in this article.

WHY USE COMPOUNDED HRT

- There are no bioidentical testosterone products for women (i.e. very low dose)
- The only approved bioidentical progesterone (other than vaginal gels) is in peanut oil
- Giving three separate products is confusing and difficult to maintain-combining E/P/T makes it easier to administer
- Being able to change the ratios allows better normalization of hormone levels
- Carriers can be individualized for sensitive patients
Problems with Compounded HRT

- More opportunity for errors in the formulation
- No studies of individual products for absorption and metabolism-necessitating monitoring of levels
- Carriers may be better or worse
- No monitoring for post-production problems, contamination, dosing errors-you and your patient have to be aware of side effects
Typical dose of Bi-est

- 80% oestriol and 20% oestradiol
- 2.5mg dose=2mg oestriol and .5mg oestradiol

How does this dose compare to FDA approved patch?
Comparison of Major symptoms: Compounded BHRT vs Commercially available HRT

<table>
<thead>
<tr>
<th>Compounded Bioidentical</th>
<th>Commercially available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain 37.2%</td>
<td>Weight gain 56.2%</td>
</tr>
<tr>
<td>Breast Tenderness 19.2%</td>
<td>Breast tenderness 54.5%</td>
</tr>
<tr>
<td>Bloating 23.1%</td>
<td>Bloating 40%</td>
</tr>
<tr>
<td></td>
<td>Mood swings 36.4%</td>
</tr>
</tbody>
</table>

A Safety and Efficacy Study of the Combination Estradiol and Progesterone to Treat Vasomotor Symptoms (REPLENISH)

This study is currently recruiting participants. (see Contacts and Locations)

Verified May 2015 by TherapeuticsMD

Sponsor:
TherapeuticsMD

Information provided by (Responsible Party):
TherapeuticsMD

ClinicalTrials.gov Identifier:
NCT01942668

First received: September 5, 2013
Last updated: May 5, 2015
Last verified: May 2015

Purpose

This study will be a prospective, randomized, double-blind, placebo-controlled, parallel group, multicenter trial of postmenopausal subjects with an intact uterus.
This author’s extensive review of the most respected HRT literature concluded that estradiol plus progesterone (bioidentical hormones) given transdermally is the safest form of HRT.
How should you administer hormones:

- Transdermally if possible
- Occasionally orally
- Rarely by injection or pellet
Effect of E2/P vs CEE/MPA on Normal Breast Cell Division

How much hormone should you give?

Enough to return levels to normal for age
Findings indicate that natural menopause appears to have no major impact on health or health behavior.
OESTRIOL
My Conclusions about Oestriol

• There is very little evidence to support the theory that oestriol in combination with other oestrogens modifies the risk of breast cancer. Oestriol is an ER-β agonist but then so are equilin and equilinin!

• Oestriol by itself has some potential as hormone therapy, but is not as effective as oestradiol and must be given in much higher doses (10:1) and therefore must be metabolized (phase 2 and excretion) by an already potentially stressed system. In high doses it MAY antagonise EGF effects.

• The combination of oestriol with other oestrogens like oestradiol by mouth may act as a competitive inhibitor of the positive effects of oestradiol on other organs (bone, brain) and therefore would require higher doses of both to be effective-- but there is little evidence one way or the other.

• High doses of oestriol (2mg or more) may not be enough to block oestradiol and is enough to stimulate the endometrium requiring a progestogen.

• Oestriol vaginal cream or suppositories have significant research to support their use. The vagina reacts differently than other tissues to oestriol and vaginal oestriol in these doses does not require a progestogen to protect the endometrium.
Specific pharmacological inhibition of GPR30 might become a promising targeted therapy for TNBC (triple negative breast cancer) in future.
But cancer cells have senescent mitochondria and lose sensitivity to ERβ agonists like oestriol.
Progesterone
Functions of Progesterone

- Down-regulation of oestrogen Receptors
- Inhibition of ER transcription at DNA
- Effects on cellular Adhesion
- Cellular Differentiation
- Apoptosis promoting
- Induction of enzymes important in oestrogen metabolism
- Priming of cellular cross-talk
- Involved in initiation of ovulation
- Inhibits uterine activity
- Involved with intracellular adhesion molecules
The Difficulty Studying Progesterone

“A topic that appears complex is actually much more complex than it appears.”

-unknown
Progestins are NOT Progesterone!
Progesterone’s effect on cell cycling is complex
Proliferation of breast epithelial cells in healthy women during the menstrual cycle

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Stockholm and Huddinge, Sweden

OBJECTIVE: Our objective was to assess proliferation in normal breast epithelial cells from healthy women during the follicular and luteal phases of the menstrual cycle.

STUDY DESIGN: We analyzed the proliferation marker Ki-67/MIB-1 by immunocytochemical methods in breast epithelial cells procured through fine needle aspiration biopsy from 47 healthy volunteers. Differences were assessed by Wilcoxon rank sum tests and correlations were determined by Spearman's rank correlation coefficient.

RESULTS: The proportion in the follicular phase (1.66%) was higher than in the luteal phase (0.31%) (p = 0.003). In ovulating women, proliferating cells increased during the follicular phase and decreased during the luteal phase (p < 0.05).


Key words: Breast epithelial cell proliferation, hormone regulation, menstrual cycle

The hormonal regulation of proliferation in the normal breast is controversial and incompletely understood. Estrogen is generally accepted as a promoter of breast epithelial cell proliferation and is thought to be involved in the development and growth of breast cancer. The controversy concerns the action of progesterone-progesterone for which the literature offers a huge number of conflicting results. Most in vitro studies of breast cancer cell lines and cultured normal cells show progesterone-progesterone to have an inhibitory effect on proliferation, whereas some indicate an independent, additive or synergistic effect in combination with estrogen. In vivo experiments so far have mainly analyzed on mitotic activity during the menstrual cycle.

Fine needle aspiration biopsy is an established technique for the preoperative diagnosis of palpable lumps in the breast. Aspirated cells can also be used for immunocytochemical analyses of estrogen and progesterone receptor content. The development of monoclonal antibodies against cell proliferation specific antigens also has made it possible to assess proliferation in cytologic breast cell samples.

The Ki-67/MIB-1 monoclonal antibody reacts with a human nuclear antigen that is present in proliferating cells but absent in quiescent cells. Cell cycle analysis

“Data clearly support a proliferative action for cyclic progesterone.”
Cell Proliferation in Breast

(a) Serum estradiol and progesterone levels

(b) Thymidine labeling index

(c) Mitotic rate

Thymidine labeling

Mitotic rate

Cycle week 1-4
What about natural progesterone being safer?
Effect of Progesterone on Breast Mitosis

Cellular environments that increase signaling from peptide growth factors

Fig. 4. The biphasic action of progesterone on breast cells, deduced from Groshong et al.© RCOG 1999 Br J Obstet Gynaecol 106, 1006–1018.
...progesterone pretreatment promotes a switch from growth driven primarily by steroid hormones to growth driven primarily by peptide growth factors.

Lange CA. Molecular Endocrinology 1999;13(6):829
What this means...

- When there is a lot of oestrogen around cyclic progesterone allows the breast cells to differentiate

- When there is less oestrogen (as in normal menopause) PR’s are not upregulated and continuous progesterone prevents cycling

- Progesterone can regulate cross talk with peptide growth factors (insulin, IGF-1) and may contribute to putting diabetics at increased risk

- GR have many different effects in the cell cycle and artificial progestins may or may not engage them depending upon the progestin.
Table 3. Adjusted Odds* of Having Higher Symptom Scores for Each Treatment Group (Row) Compared With an Alternative Treatment Group (Column)

<table>
<thead>
<tr>
<th>Treatment assignment¹ and symptom group</th>
<th>Comparison group⁴,⁸</th>
<th>Placebo</th>
<th>CEE + MPA (cyc)</th>
<th>CEE + MPA (con)</th>
<th>CEE + MP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast discomfort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEE</td>
<td>1.16 (0.70, 1.93)</td>
<td>0.52 (0.33, 0.82)</td>
<td>0.61 (0.38, 0.98)</td>
<td>0.50 (0.32, 0.79)</td>
<td></td>
</tr>
<tr>
<td>CEE + MPA (cyc)</td>
<td>2.27 (1.39, 3.56)</td>
<td>1.17 (0.76, 1.81)</td>
<td>0.97 (0.63, 1.46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEE + MPA (con)</td>
<td>1.92 (1.16, 3.09)</td>
<td>1.31 (0.87, 1.95)</td>
<td>0.83 (0.53, 1.26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEE + MP</td>
<td>2.33 (1.46, 3.74)</td>
<td>0.92 (0.63, 1.35)</td>
<td>0.80 (0.54, 1.18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perceived weight gain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEE</td>
<td>0.80 (0.54, 1.19)</td>
<td>1.15 (0.78, 1.71)</td>
<td>1.31 (0.87, 1.95)</td>
<td>0.92 (0.63, 1.35)</td>
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<tr>
<td>CEE + MPA (cyc)</td>
<td>0.69 (0.47, 1.03)</td>
<td>1.13 (0.87, 1.70)</td>
<td>0.80 (0.54, 1.18)</td>
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<tr>
<td>CEE + MPA (con)</td>
<td>0.61 (0.41, 0.91)</td>
<td>1.31 (0.87, 1.95)</td>
<td>0.70 (0.47, 1.05)</td>
<td></td>
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<tr>
<td>CEE + MP</td>
<td>0.87 (0.60, 1.26)</td>
<td>0.92 (0.63, 1.35)</td>
<td>0.80 (0.54, 1.18)</td>
<td></td>
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<tr>
<td>Perceived weight loss</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEE</td>
<td>1.22 (0.61, 2.46)</td>
<td>0.80 (0.41, 1.55)</td>
<td>0.66 (0.35, 1.26)</td>
<td>0.55 (0.29, 1.02)</td>
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<tr>
<td>CEE + MPA (cyc)</td>
<td>1.52 (0.78, 2.97)</td>
<td>0.82 (0.45, 1.49)</td>
<td>0.68 (0.38, 1.20)</td>
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<tr>
<td>CEE + MPA (con)</td>
<td>1.85 (0.97, 3.56)</td>
<td>0.82 (0.45, 1.49)</td>
<td>0.83 (0.47, 1.45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEE + MP</td>
<td>2.22 (1.17, 4.30)</td>
<td>0.82 (0.45, 1.49)</td>
<td>0.83 (0.47, 1.45)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Odds ratios are adjusted for baseline symptom level, clinical site, and uterus status.

¹ CEE = 0.625 mg conjugated equine estrogens (daily); CEE + MPA (cyc) = 0.625 mg conjugated equine estrogens (daily) and 10 mg medroxyprogesterone acetate (days 1–12); CEE + MPA (con) = 0.625 mg conjugated equine estrogens (daily) and 2.5 mg medroxyprogesterone acetate (daily); CEE + MP = 0.625 mg conjugated equine estrogens (daily) and 200 mg micronized progesterone (days 1–12).

⁴ Entries in table are odds ratios with 95% confidence intervals from generalized Wald tests in parentheses.

⁸ N = 858–862 (due to missing data); N randomized to each arm: placebo (174); CEE (175); CEE + MPA (cyc) (174); CEE + MPA (con) (174); CEE + MP (178).
<table>
<thead>
<tr>
<th>HRT type and duration of exposure (years)</th>
<th>Cases/PY</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>None</strong></td>
<td>766/244,632</td>
<td>1.29 (1.02–1.65)</td>
</tr>
<tr>
<td>Estrogen alone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td>24/6,747</td>
<td>1.26 (0.83–1.89)</td>
</tr>
<tr>
<td>[2–4]</td>
<td>18/5,705</td>
<td>1.13 (0.70–1.81)</td>
</tr>
<tr>
<td>[4–6]</td>
<td>14/3,172</td>
<td>1.50 (0.88–2.56)</td>
</tr>
<tr>
<td>6+</td>
<td>13/3,301</td>
<td>1.31 (0.76–2.28)</td>
</tr>
<tr>
<td><strong>p for trend</strong></td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>Estrogen + progesterone</td>
<td>129/40,537</td>
<td>1.00 (0.83–1.22)</td>
</tr>
<tr>
<td>&lt;2</td>
<td>18/8,697</td>
<td>0.71 (0.44–1.14)</td>
</tr>
<tr>
<td>[2–4]</td>
<td>33/11,647</td>
<td>0.95 (0.67–1.36)</td>
</tr>
<tr>
<td>[4–6]</td>
<td>30/7,619</td>
<td>1.26 (0.87–1.82)</td>
</tr>
<tr>
<td>6+</td>
<td>43/10,111</td>
<td>1.22 (0.89–1.67)</td>
</tr>
<tr>
<td><strong>p for trend</strong></td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Estrogen + dydrogesterone</td>
<td>108/31,045</td>
<td>1.16 (0.94–1.43)</td>
</tr>
<tr>
<td>&lt;2</td>
<td>16/6,923</td>
<td>0.84 (0.51–1.38)</td>
</tr>
<tr>
<td>[2–4]</td>
<td>28/8,697</td>
<td>1.16 (0.79–1.71)</td>
</tr>
<tr>
<td>[4–6]</td>
<td>21/5,590</td>
<td>1.28 (0.83–1.99)</td>
</tr>
<tr>
<td>6+</td>
<td>35/7,876</td>
<td>1.32 (0.93–1.86)</td>
</tr>
<tr>
<td><strong>p for trend</strong></td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>Estrogen + other progestagens</td>
<td>527/104,243</td>
<td>1.69 (1.50–1.91)</td>
</tr>
<tr>
<td>&lt;2</td>
<td>86/22,792</td>
<td>1.36 (1.07–1.72)</td>
</tr>
<tr>
<td>[2–4]</td>
<td>134/30,189</td>
<td>1.59 (1.30–1.94)</td>
</tr>
<tr>
<td>[4–6]</td>
<td>106/19,942</td>
<td>1.79 (1.44–2.23)</td>
</tr>
<tr>
<td>6+</td>
<td>156/23,817</td>
<td>1.95 (1.62–2.35)</td>
</tr>
<tr>
<td><strong>p for trend</strong></td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Weak estrogens¹</td>
<td>56/17,091</td>
<td>0.90 (0.68–1.18)</td>
</tr>
<tr>
<td>Others⁴/unknown HRT</td>
<td>82/21,071</td>
<td>1.27 (1.01–1.60)</td>
</tr>
<tr>
<td>Mixed⁵</td>
<td>538/130,594</td>
<td>1.25 (1.11–1.41)</td>
</tr>
</tbody>
</table>
Negative effects of supra-physiologic levels of progesterone:

- Oversaturation of tissues or receptors causing persistent progesterone receptors
- Oestrogen receptor down-regulation
- Over production of downstream metabolites (cortisol)
- Over production of intermediate signalling molecules (WNT, RANKL)
Production of hormones in Pregnancy

- Progesterone (serum) increases by factor of 4
- Oestriol (serum) increases by factor of 20
- Pregnant urine $E3/E1+E2 = 10:1$ (Non-pregnant urine $E3/E1+E2 = 1:1$)
- Daily production of $E3=80mg$
- **Daily production of Progesterone 300mg**

Progesterone and the Heart
Progestogens and Coronary Plaque

Effect of Progesterone vs Progestin on Coronary Plaque

Mikkola TS, Clarkson TB, Cardiovascular Research 53 (2002) 605-619
Testosterone
# Natural vs. surgical menopause

## Table 1. Mean Steroid Levels in Women Normalized to pg/mL

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Reproductive Age</th>
<th>Natural Menopause</th>
<th>Surgical Menopause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol</td>
<td>150</td>
<td>10-15</td>
<td>10</td>
</tr>
<tr>
<td>Testosterone</td>
<td>400</td>
<td>290</td>
<td>110</td>
</tr>
<tr>
<td>Androstenedione</td>
<td>1,900</td>
<td>1,000</td>
<td>700</td>
</tr>
<tr>
<td>DHEA</td>
<td>6,000</td>
<td>2,000</td>
<td>1,800</td>
</tr>
<tr>
<td>DHEA-S</td>
<td>3,000,000</td>
<td>1,000,000</td>
<td>1,000,000</td>
</tr>
</tbody>
</table>

DHEA = dehydroepiandrosterone; DHEA-S = DHEA sulfate.

The risk for breast cancer increased statistically significantly with increasing concentrations of all sex hormones examined (including testosterone). SHBG was associated with a decrease in breast cancer risk \(P(\text{trend}) = .041\).
HRT without Testosterone

- Conventional HT (absent testosterone) produces an imbalance between E2/T by suppressing gonadotropin production of androgens and simultaneously up-regulating SHBG.¹

Can you think of something else that lowers Testosterone?
Take home messages about Testosterone

- **Ideal range in menopause 0.25 - 0.40 ng/mL**

- Can be used to modulate SHBG and therefore oestrogen.

- Not a cause of loss of libido in women as often as we would like to think, although the balance between oestrogen and testosterone is important.

- Can increase the risk of breast cancer, however this may depend on its conversion to estradiol, its effect on SHGB and its association with insulin resistance.

- Is likely a marker for adrenal function when low.
Take Home Messages

- Bioidentical transdermal oestrogen is better than oral oestradiol or oral conjugated equine oestrogens.

- Bioidentical progesterone is superior to chemical progestins for both breast health and cardiovascular health.

- If you are mimicking mother nature (HRT) start low and go up slowly to reach normal for age.

- If you are giving hormones to treat symptoms only (HT) use the smallest possible dose for the shortest period of time.
If you don’t remember anything else…

- Stressors
- Toxins
- Antigens, Allergens
- Inflammation, Infections
- Nutrition
- Sleep. Sedentary lifestyle
Here's Your Prescription
Nutritional Plan for Menopause

Always try to go here first!
Protein/Carbohydrate Balance
Treat obesity and DM2
Treat insulin Resistance

- Decreases inflammation
- Decreases oestrogen production in fat
- Improves oestrogen metabolism
- Decreases oxidative stress
Treat Inflammation
Crucifers!
Vegetables not Fruit
Good fat not bad fat!
Fatigue, decreased steroid production

Proper care of Mitochondria
Supplements
It's like your mother told you:
Get enough sleep!
Move your body!
The moral: The safest way to treat the system it to allow it to rebalance itself.
The End

Thank you