Hormone Replacement in Women: Promise and Pitfalls

Bethany Hays MD

SO MANY ARTICLES... SO LITTLE TIME!
Outline

• What is BHRT?
• Problems with the standard of care
• Who needs hormone therapy?
• Estrogen/progesterone and testosterone-what to give, what route, how much?
• Laboratory evaluation-what to use and when to use it?
• How I give HRT
• Summary
What is bio-identical hormone therapy

Identical...well almost!
Terminology confusing to patients:

In a recent survey at a compounding pharmacy:

- Of 82 women surveyed:
  - 74 (90%) had heard of BHRT
  - 37 (45%) used them
  - 50% thought natural meant “not synthetic/not man-made/no chemicals”
  - 45% thought BHRT meant “plant derived”
  - 11% thought BHRT meant “identical to human hormones”

BHRT

• Associated with compounded formulas
• Associated in the U.S. with the use of estriol (in Europe there are pharmaceutical versions of oral and trans-vaginal estriol)
• Associated with claims of safety and efficacy that are unfounded or poorly supported by the evidence (and some claims that are perfectly correct and well-supported).
• Associated with the use of testosterone trans-dermally for women.
Bio-identical=identical to what is made and metabolized in the human female
Natural = made in nature
And just to be clear...this one is not bioidentical AND not made in nature!
Compounding is a separate issue!
Standard of Care

Knowing when you are on thin ice.
Know the “Standard of Care”

• North American Menopause Society (NAMS) now recommends calling it “Hormone Therapy” (HT) rather than “Hormone Replacement Therapy” (HRT)
• ACOG and the FDA recommends: Replace the “smallest amount of hormone for the shortest period of time.”
• When the uterus is absent give only estrogens.
• Don’t give testosterone unless you are willing to give oral methyltestosterone (combined with CEE) since that is the only FDA approved testosterone for women, however this drug (in the doses given to men) causes liver cancer.
NAMS and ACOG position in translation:

• Hormones are not safe so you should use the smallest amount possible for the shortest period of time
• Progestins are not safe so don’t give them unless you have to to prevent endometrial cancer
• Don’t give testosterone
American Association of Clinical Endocrinologists:

• “In summary, there is no scientific evidence that specific combinations of oral estrogens provide improved safety or efficacy compared to FDA-approved pharmaceutical products in the treatment of menopausal females. Additional clinical and basic research of this subject is needed.”

• “There is inadequate research to say that specific combinations [Bi-est and Tri-est] are safer than (some) FDA approved pharmaceutical products [such as transdermal estradiol patch or oral progesterone] in the treatment of menopausal females. Additional clinical and basic research of this subject is needed.”
American Association of Clinical Endocrinologists in translation:

- All estrogens are created equal but some are not available in FDA approved forms.
- Since we have FDA approved transdermal and oral estrogen, and oral progesterone, they are safe.
- Anything else is probably not safe since there is not enough information.
HT or HRT?

• Currently, HRT has been replaced with the term HT (hormone therapy) with the emphasis on the “therapy” with defined risks and benefits and a(n unclear) limit on the length of exposure.
• “Every menopausal woman should have an individualized risk-benefit evaluation to determine whether HT suits her need.”

The problem is...

What if her risks and her needs are at odds with each other?
To summarize: in my words...

- There is inadequate research for many hormone combinations leading to the belief that all estrogens are created equal, although there is adequate research to say that transdermal or trans-vaginal preparations of estradiol are safer than oral estradiol, estrone, or CEE.
- There is inadequate research (no large RCT’s) to say that progesterone is safer than progestins in humans, although there is adequate research to say that progestins are not safe (WHI, HERS) and some evidence that progesterone is safer (PEPI trial).
- There are no FDA approved, bioidentical testosterone products and no transdermal testosterone products available for women, although there are for men; there is evidence that in some women, testosterone is helpful and some biological knowledge to say that it may decrease the amount of estradiol and testosterone therapy needed (by lowering SHBG).
Standard Care

- Treat symptoms
- Do not measure hormone levels (they are inaccurate, they fluctuate, and you can’t measure CEE’s and progestins anyway)
Problems with *standard* care: Treating symptoms alone

- Treating symptoms only, may not leave the body in best hormonal balance, leaving it vulnerable to further imbalances.
- Many of the symptoms (hot flashes) while responsive to HT are not CAUSED by hormone deficiency but rather by endocrine and system-wide imbalances that the system is trying to deal with as best it can.
- Therefore, unless the system is rebalanced these symptoms may never go away and you never get those women off hormones comfortably.
When should abnormal labs not be treated with HRT?—Out of range? Think STRANGE!
Evaluating the Matrix

Before leaping to hormone therapy
<table>
<thead>
<tr>
<th>Detoxification and Biotransformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxidative/Reductive Homeodynamics (Mitochondrial function)</td>
</tr>
<tr>
<td>Immune Surveillance and Inflammatory Process</td>
</tr>
<tr>
<td>Hormone and Neurotransmitter regulation</td>
</tr>
<tr>
<td>Digestion and Absorption</td>
</tr>
<tr>
<td>Structural/Boundary/Membranes</td>
</tr>
<tr>
<td>Psychological and Spiritual Equilibrium (MIND-BODY)</td>
</tr>
</tbody>
</table>
$ \beta^1 \Rightarrow $

7 \rightarrow \beta \Rightarrow

6 \rightarrow 0 \rightarrow \beta \Rightarrow$
A Framework for Assessment of Hormone and Neurotransmitter Regulation

A brief review from AFMCP
First listen to your patients!

Doctor, couldn't it be something to do with my diet that's causing these problems?

Now you are being delusional again. It must be to do with some deep underlying psychological problem. I'll switch you to Prozac. Let's see if that helps a bit.
First, what presenting signs and symptoms suggest a hormonal imbalance?

Examples may include:

• Mood swings (Could be many other things)
• Breast tenderness
• Heavy periods
• Anxiety (Could be many other things)
• Sleep disruption (Could be many other things)
• Hot flashes (Likely autonomic dysfunction)
• Irregular bleeding
• Low libido (Could be many other things)
• Brain fog (Could be many other things)
• Infertility (Could be many other things)
• Vaginal dryness (Could be many other things)
• Weight gain (Could be many other things)
Basically, patients come in with:

- Hot flashes
- Brain fog
- Symptoms of rapid hormone change or fluctuation (anxiety/depression, fatigue, brain fog)
- Weight gain
- Vaginal dryness and it’s urogenital complications
- Loss of libido
- The belief that “hormones are the problem and HRT will help!”
The questions for the clinician:

• Are her complaints due to hormone deficiency?
• Which hormones should I replace?
• Can I improve symptoms of an estrogen-affected immune or neurological problem (MS and other TH-1 diseases)?
• Can I protect my patient from age-related problems by giving hormones?
Detoxification and Biotransformation

Immune Surveillance and Inflammatory Process

Oxidative/Reductive Homeodynamics

FUNCTIONAL MEDICINE MATRIX MODEL™

E affects TH1 and TH2

Progesterone supports cortisol levels

CYP enzymes metabolize hormones

P slows motility

Dysbiosis affect E metabolism

E,P,T interact with all other hormones esp. adrenals

E affects levels of neurotransmitters, is involved in sexual identity

Estrogen IS an antioxidant

Digestion and Absorption

Hormone and Neurotransmitter Regulation

Psychological and Spiritual Equilibrium

Structural/Boundary/Membranes

Exercise

Beliefs & Self-Care

Relationships

Nutrition Status

Sleep

Date: ______  Name: ___________________  Age ______  Sex______  Chief Complaints: _____________________________________
FUNCTIONAL MEDICINE MATRIX MODEL™

Detoxification and Biotransformation

Immune Surveillance and Inflammatory Process

Oxidative/Reductive Homeodynamics (Mitochondrial function)

Detoxification and Biotransformation

SNP’s for CYP450’s affect estrogen metabolism

Hormone and Neurotransmitter regulation

Digestion and Absorption

B-glucuronidase increases enterohepatic circulation

Psychological and Spiritual Equilibrium (MIND-BODY)

Stress steals progesterone and anxiety necessitates progesterone

Structural/Boundary/Membranes

Hormones “talk” to each other

The Patient’s Story Retold

Antecedents (Predisposing)

SNP’s for CYP450’s

Triggering Events (Activation)

SEE NEXT SLIDE

SEE NEXT SLIDE

SEE NEXT SLIDE

Nutrition Status

Exercise

Sleep

Beliefs & Self-Care

Relationships

Alcohol increases 16OH estrogen SAD and obesity

Over or under exercising can affect stress cascades

Many religions make women believe they are second-class citizens

Relationship with spouse affects libido

Raised adrenalin and increases hot flashes

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Date: ____ Name: ___________________ Age _____ Sex______ Chief Complaints: ___________________________________
Second, what specific antecedents, triggers, and mediators may impinge on optimal hormonal function?

**Antecedents** may include:
- Genetic SNP (MTHFR, COMT, CYP1B1, GST-M1)
- Toxins/xenobiotics (PCBs, pesticides, xenohormones)
- Prenatal programming and toxic exposure

**Triggers** may include:
- Menopause/Perimenopause
- Gut health
- Nutritional insufficiency (cofactor, etc.)
- Hx of synthetic hormone use (OCPs, DES, infertility treatment)
- Hx of physical/sexual abuse
- Pregnancies
- Surgery

**Mediators** may include:
- Chronic stress
- Loss of ‘meaning’/spiritual emptiness/loss of connection/loss of relationships
- Nutrition
- Other endocrine disruptions
Third, how may these antecedents, triggers, and mediators affect hormonal function in these particular areas:

- **Production/synthesis** of the hormone
- **Transport/distribution/interaction** with other hormones
- **Sensitivity** of the hormone/receptor sensitivity to the message
  - Actions in the cell and the organism
  - Interaction of that hormone with other hormones
- **Detoxification** of that hormone
  - Excretion of that hormone
Production/synthesis and secretion of the hormone

Transport/conversion/distribution/ interaction with other hormones

Cellular sensitivity to the hormone signal

Detoxification/excretion of the hormone
Fourth, what laboratory evaluation would be useful to evaluate this hormonal imbalance?

Examples:

• Estrone, estradiol, estriol, total and/or free testosterone, progesterone, SHBG
• Adrenal function testing
• Thyroid hormone testing
• Glucose, insulin, triglycerides, etc.
• GI evaluation
Fifth, based on this information, how would you intervene?

Examples may include:

• Diet
• Sleep
• Stress reduction and spiritual support recommendations
• Nutritional supplementation
• Botanicals
• Hormone replacement therapy (HRT)
• Pharmaceuticals
• Surgery
Sixth, how do you follow these patients?
Examples may include:

- Hormone testing—which to test and how often
- Physical examination—appearance of skin, hair, breast tissue, vaginal epithelium
- Assessment of improvement of signs or symptoms—growth of fibroids, vaginal bleeding, PMS, irritability, libido
- Changes in mammogram or thermogram
Who needs hormone (replacement) therapy?
Oophorectomy

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

Don’t menopausal hormones come from the periphery?
Natural vs. Surgical Menopause

<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.

% of hormone remaining
50%/36%
33%/30%
Ovarian hormone contribution after menopause

**TABLE 2.** Mean (range) concentrations of T, A, DHEA, E1, and E2 from ovarian venous and intraoperative peripheral serum

<table>
<thead>
<tr>
<th></th>
<th>Ovarian</th>
<th>Peripheral</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T (ng/ml)</td>
<td>7.2 (0.2–62.0)</td>
<td>0.3 (0.2–0.8)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>A (ng/ml)</td>
<td>4.3 (0.0–21.7)</td>
<td>1.1 (0.6–1.6)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>DHEA (ng/ml)</td>
<td>8.8 (3.6–33.8)</td>
<td>5.2 (2.0–9.0)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>E1 (pg/ml)</td>
<td>150 (24–1276)</td>
<td>50 (24–88)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>E2 (pg/ml)</td>
<td>99 (5–834)</td>
<td>15 (4–32)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Fold difference = ovarian venous/peripheral.
What have we learned from oophorectomy?
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\(^3,4,5\)
References for “Risk of Oophorectomy”


Effect of oophorectomy

- Increased death from all causes\textsuperscript{1}
- Increased risk of all cancers except ovarian cancer\textsuperscript{2,3}.
References for “Effect of Oophorectomy”

In other words:

- Among healthy women hysterectomized before age 55 (most), 8.6% more would be alive at age 80 if their ovaries were conserved\(^1\).
- Removing the ovary prior to age 50 takes 8 years off a woman’s life.
- The earlier you remove the ovary the more it affects a woman’s health in the long term.

So clearly, women who lose their ovaries deserve replacement...but how many women is that?
Oophorectomy

• 78% of women aged 45 to 64 and 55% of all women undergo oophorectomy.
• Almost 300,000 women undergo bilateral oophorectomy each year.

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 normally?
Does hysterectomy with ovarian preservation affect ovarian function

- Part of the blood supply for the ovary comes through the utero-ovarian ligament.
- Manipulation of the ovarian artery may cause spasm.
- In a prospective study, after 5 years of follow-up, 20% of women who underwent simple hysterectomy went through menopause vs 7% of an age matched control group.¹
- Menopause occurs on average 4 years earlier after hysterectomy
Citations for Previous Slide-Does hysterectomy with ovarian preservation affect ovarian function


Testosterone Levels Following Hysterectomy +/- Oophorectomy

...so how many women is that?
Hysterectomy

• 600,000 hysterectomies done each year
• 41% of women in WHI had hysterectomy\(^1\)
• 55% of women with hysterectomy lose both ovaries\(^2\)
• Unknown number have damage to ovarian function.
References for previous slide—“Hysterectomy”


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
• Possible damage to utero-ovarian blood supply
• Adhesions or pelvic congestion as additional etiologies of symptoms
• Although menstrual periods did not change significantly, salivary progesterone levels declined.³
Citations for previous slide “Post Tubal Ligation syndrome”


Autoimmune Oophoritis
Ovarian autoimmunity – is it an issue after menopause?

• General tendency for women to have more autoimmune diseases
• Autoimmune thyroid disease as evidence of endocrine autoimmunity
• POF and autoimmunity is a known cause of infertility
Autoimmune effects on ovarian hormone output

- Women with autoimmune oophoritis have been shown to have high inhibin B and low estradiol. This causes suppressed FSH relative to LH although both are elevated.
- Many of these women also have adrenal cortical antibodies and some develop adrenal failure as well.
- In premenopausal women there is selective dysfunction of the theca cells

### Table I

<table>
<thead>
<tr>
<th>Authors</th>
<th>Frequent associations</th>
<th>Occasional associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crispell and Parson, 1952</td>
<td>Thyroid diseases</td>
<td>Hypoparathyroidism</td>
</tr>
<tr>
<td>Guinet and Pommateur, 1954</td>
<td>APS-II</td>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>Rupp and Paschis, 1955</td>
<td>APS-I</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Turkington and Lebovitz, 1967</td>
<td>Addison’s disease</td>
<td>Periculous anaemia</td>
</tr>
<tr>
<td>Vazquez and Kenny, 1973</td>
<td></td>
<td>Vitiligo</td>
</tr>
<tr>
<td>Rebar et al., 1982</td>
<td></td>
<td>Alepecia areata</td>
</tr>
<tr>
<td>Coulam, 1983</td>
<td></td>
<td>Crohn’s disease</td>
</tr>
<tr>
<td>Aiman and Smentek, 1985</td>
<td></td>
<td>Ulcerative colitis</td>
</tr>
<tr>
<td>Aiper and Garner, 1985</td>
<td></td>
<td>Coeliac disease</td>
</tr>
<tr>
<td>LaBarbera et al., 1988</td>
<td></td>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td>Betterle et al., 1993</td>
<td></td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Kim et al., 1995</td>
<td></td>
<td>Juvenile idiopathic arthritis</td>
</tr>
<tr>
<td>Conway et al., 1996</td>
<td></td>
<td>Primary biliary cirrhosis</td>
</tr>
<tr>
<td>Betterle and Volpato, 1998</td>
<td></td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>Packham and Hall, 2003</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

APS = autoimmune polyglandular syndrome.

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

Who else might legitimately need hormone therapy?
I’m still hot, it just comes in flashes now.
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
Citations for “Danger of Hot Flashes”


These data are consistent with our theory of elevated sympathetic activation as a trigger for menopausal hot flashes and with previous work on heart rate variability during the stages of sleep.
Other Treatments for hot flashes

• Magnesium oxide 800mg showed benefit in more than half of patients being treated for breast cancer.¹
• SNRI’s- affect norepinephrine levels (Venlafaxine)
• Gabapentin (GABA opposes adrenalin)
• Stellate ganglion block relieved hot flashes by interrupting sympathetic/central connections.²
• Acupuncture may improve symptoms and quality of life in breast cancer survivors.³,⁴
• AND LOOK OUT here comes another use for statins!⁵
• Rhubarb, red clover, black cohosh, Maca
• Non-GMO soy not well supported in literature but works for some.
Citations for previous slide: “Other Treatments for hot flashes”


2. Lipov EG, Lipov S, Joshi JR, Santucci VD, Slavin KV, Beck Vigue SG. Stellate ganglion block may relieve hot flashes by interrupting the sympathetic nervous system. Med Hypotheses. 2007 Apr 9; [Epub ahead of print]


It is important to remember that hot flashes do not always correlate with estrogen levels...

So estrogen is not always the correct treatment!
Perimenopause

A time of hot flashes with paradoxically high estrogens.
Hot Flashes and Drops in Estrogen Levels

Cyclic Vasomotor Symptoms

Perimenopausal fluctuation in hormones

Relative hyperestrogenism and relative decrease in progesterone during perimenopause, as shown by daily urine sampling.
Norm = midreproductive-aged women (controls)
Peri = perimenopausal women
Day 0 = day of LH surge
mgCr = mg creatinine
PDG = pregnanediol glucuronide
E1 = estrone conjugates

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

The role of isoflavones.

- Vaginal Bleeding
- Hot Flashes

E2 level required for bleeding
Perimenopause

- Women have trouble with changing hormone levels
- Perimenopausal levels of estrogen are elevated
- Perimenopausal fluctuations in hormones last beyond the last menstrual period
LOOP Events: Luteal Out of Phase Events

Many of the marked increases in ovulatory cycle E2 and cycle irregularities during the menopausal transition may be due to LOOP events and appear to be triggered by prolonged high follicular phase follicle-stimulating hormone levels

Hale GE, Hughes CL, Burger HG, Robertson DM, Fraser IS. Menopause. 2009 Jan-Feb;16(1):50-9
Loop Estradiol Level
Case study: Perimenopausal woman with Loop event

- 46 yo WMF with heavy irregular periods, anemia, and fibroids was referred for control of her menstrual bleeding after an episode of prolonged heavy bleeding that took her Hct to 32.0 and Hgb to 10.0
- “Should I have an endometrial ablation?”
LOOP events in perimenopause:

46 yo WMF with heavy periods

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Reference Range</th>
<th>Reference Range</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progesterone</td>
<td>7.75</td>
<td>0.95-21.00 ng/mL</td>
<td></td>
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</tbody>
</table>

**Binding Proteins**

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Reference Range</th>
<th>Reference Range</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex Hormone Binding Globulin</td>
<td>178</td>
<td>18-111 nM/mL</td>
<td></td>
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</tbody>
</table>

**Androgens**

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Reference Range</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHEA-S</td>
<td>36</td>
<td>35-430 mcg/dL</td>
</tr>
<tr>
<td>Testosterone</td>
<td>0.25</td>
<td>0.10-0.80 ng/mL</td>
</tr>
<tr>
<td>Free Androgen Index</td>
<td>0.48</td>
<td>0.43-8.48</td>
</tr>
</tbody>
</table>

**Estrogens**

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Reference Range</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrone Sulfate (E1S)</td>
<td>2.02</td>
<td>0.75-4.28 ng/mL</td>
</tr>
<tr>
<td>Estrone (E1)</td>
<td>171</td>
<td>25-63 pg/mL</td>
</tr>
<tr>
<td>Estradiol (E2)</td>
<td>504</td>
<td>27-246 pg/mL</td>
</tr>
<tr>
<td>Estriol (E3)</td>
<td>&lt;80</td>
<td>≤50 pg/mL</td>
</tr>
</tbody>
</table>

**Estrogen Metabolism**

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Reference Range</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Hydroxyestrone</td>
<td>&gt;2000</td>
<td>112-355 pg/mL</td>
</tr>
<tr>
<td>16α-Hydroxyestrone</td>
<td>NR</td>
<td>1.3-680 pg/mL</td>
</tr>
<tr>
<td>2/16α-Hydroxy-Estrone Ratio</td>
<td>NR</td>
<td>0.40-1.40</td>
</tr>
</tbody>
</table>
Case study: Perimenopausal woman with Loop event

• Patient was sent to oncology surgeon.
• Ultrasound was normal.
• Repeat hormone levels done at an unknown time in her cycle was in the 239pg/mL. Although this was within range for mid-cycle it is still very high.
• I convinced them to repeat this at a known time in her cycle (and asked her to come to my office immediately afterward to get split samples from my lab of choice and the Mayo clinic which does high sensitivity estradiol testing.)
Comparison Labs

• On what turned out to be day 18 of her cycle:
  Their lab  My lab
  Estradiol  145pg/mL  109
  Estrone    115pg/mL  92

  Additionally SHBG  178→133
      16OH  526→416
      2OH   >2000→381
...after full workup and hormone modulation

### Progesterone

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Reference Range</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progesterone</td>
<td>1.46</td>
<td>0.95-21.00 ng/mL</td>
</tr>
</tbody>
</table>

### Androgens

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Reference Range</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHEA-S</td>
<td>70</td>
<td>35-430 mcg/dL</td>
</tr>
<tr>
<td>Testosterone</td>
<td>0.24</td>
<td>0.10-0.80 ng/mL</td>
</tr>
<tr>
<td>Free Androgen Index</td>
<td>0.63</td>
<td>0.43-8.48</td>
</tr>
</tbody>
</table>

### Binding Proteins

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex Hormone Binding Globulin</td>
<td>18-114 nmol/L</td>
</tr>
</tbody>
</table>

### Estrogens

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Reference Range</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrone Sulfate (E1S)</td>
<td>1.64</td>
<td>0.75-4.23 ng/mL</td>
</tr>
<tr>
<td>Estrone (E1)</td>
<td>0.92</td>
<td>28-163 pg/mL</td>
</tr>
<tr>
<td>Estradiol (E2)</td>
<td>109</td>
<td>27-346 pg/mL</td>
</tr>
<tr>
<td>Estriol (E3)</td>
<td>&lt;= 80</td>
<td>&lt;= 80 pg/mL</td>
</tr>
</tbody>
</table>

### Estrogen Metabolism

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Hydroxyestrone</td>
<td>112-656 pg/mL</td>
</tr>
<tr>
<td>16α-Hydroxyestrone</td>
<td>415</td>
</tr>
<tr>
<td>2:16α-Hydroxy-Estrone Ratio</td>
<td>0.92</td>
</tr>
<tr>
<td>16α-Hydroxy-oestrone</td>
<td>213</td>
</tr>
<tr>
<td>600-800 pg/mL</td>
<td>0.40-1.40</td>
</tr>
</tbody>
</table>
Case study: Perimenopausal woman with Loop event

• Treatment:
  1. Anti-aromatase therapies- EPA, Curcumin, anti-inflammatory diet
  2. Phase 1 detoxification- Organic diet, I3C, isoflavones from Kudzu
  3. Phase 2 detoxification- B-vitamins, sulfate containing vegetables
  4. Phase 3 detoxification- Calcium d-Glucarate
Progesterone Deficiency and PMS

- Nervous tension
- Mood swings
- Irritability
- Anxiety
- Cramping
- Bloating
- Pain
- Depression
- Insomnia
- Breast tenderness
Ways to Improve Perimenopausal Progesterone Imbalance

• Prevent cortisol steal by stress reduction
• Chaste berry herbal supplementation-decreases prolactin and may increase progesterone\(^1,2\)
• Bioidentical progesterone decreases estrogen receptors and therefore estrogen effect (progestins will not work except to decrease bleeding; OCP’s may help by lowering estrogen or hurt by lowering progesterone).  
• Isoflavones modulate estrogen levels\(^3\) and even-out the fluctuations.
• Decrease relative estrogen levels by decreasing inflammation and by improving estrogen metabolism and excretion
Citations for previous slide “Ways to Improve Perimenopausal Progesterone Imbalance”


Safety of Progesterone in Perimenopause

• Progesterone downregulates estrogen receptors and may protect women from the high levels of estrogen during LOOP Events
• While levels of estradiol in premenopausal women were associated with breast cancer risk (RR 2.1 between highest and lowest quartiles), progesterone levels were not associated with cancer risk.

Perimenopause: “Gets and Rids”

GET: PROGESTERONE
Tubal ligation, autoimmune, radiation or significant damage to the gland-get progesterone and rarely estrogen until after menopause

RID: ESTROGEN
Perimenopausal imbalance of Estrogen and Progesterone (PMS, LOOP events, menorrhagia, fibroids, endometriosis)- Modulate estrogen, adrenal support with sleep, HRV
RID: allergy elimination diet, avoid sugar, caffeine and alcohol.
RID: Environmental xenoestrogens- Look for sources and encourage detoxification
...and by the way FSH is worthless to diagnose menopause!

So to come full circle, who needs hormone therapy?
FM answer to the question:

• Women who have had an endocrine gland damaged or removed need to have the hormones produced by that gland replaced, perhaps for the rest of their lives.
• Women who have symptoms caused by imbalances that you are in the process of fixing but who need help NOW!
• Pre- or perimenopausal women who need progesterone
Prescribing Menopausal Hormone Replacement Therapy
"Menopause is easy - after you stop laying eggs, they eat you."
The FDA *generally* recommends **against** HT for women with:

- Present, past or suspected breast cancer
- Known or suspected estrogen sensitive malignancy (uterus, ovary, brain)
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- Previous idiopathic or current VTE (DVT, PE)
- Active or recent arterial thromboembolic disease (angina, MI)
- Untreated hypertension
- Active liver disease
- Known hypersensitivity to hormone or excipients
- Porphyria cutanea tarda (absolute contraindication)

From AACE “**AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS MEDICAL GUIDELINES FOR CLINICAL PRACTICE FOR THE DIAGNOSIS AND TREATMENT OF MENOPAUSE**”
One size does not fit all...
Problems with *standard* care: Only using FDA approved hormones

- Variability between patients and their ability to produce and metabolize hormones makes “one size fits all” less than ideal.
- Bioidentical hormones have a better profile of safety and effectiveness for both breast and cardiovascular risk
- They make little mention of testosterone.
What should you give?
How much to give?
How to give it?
From the original WHI report:

“It remains possible that transdermal estradiol with [orally administered] progesterone, which more closely mimics the normal physiology and metabolism of endogenous sex hormones, may provide a different risk-benefit profile.”

American Association Of Clinical Endocrinologists Medical Guidelines For Clinical Practice For The Diagnosis And Treatment Of Menopause. Endocrine Practice Vol 12 No. 3 May/June 2006 315
Estrogens

- Estrone-Sulfate
- Estrone
- Estradiol
- 16α-Hydroxy-estrone
- 2-Hydroxy-estrone
- 4-Hydroxy-estrone
- Estriol
- 2-Methoxy-estrone
- 4-Methoxy-estrone
Differences in Pre- and Post-menopausal production/metabolism of estrogens

**Pre-menopause**
- Mostly estradiol from ovary
- Production is HPO controlled
- Metabolism primarily in liver of high levels of E2 from the ovary
- Glucuronidation is more important
- Relatively low 4OH estradiol by CYP 1B1(as it is primarily expressed in peripheral tissues)

**Post-menopause**
- Mostly estrone from the periphery
- Estrogens are made from adrenal and (initially) from ovarian androgen precursors
- HPO control may exist for testosterone production initially.
- Powerful local effect but not very much going to liver so local metabolism more important
- Relatively high CYP 1B1 metabolism to 4OH estrone

Estrogen Therapy Guidelines

- Measure levels before giving extra estradiol (especially early in menopause)
- Select the estrogen(s) you wish to use
- Selection of the carrier and route of administration
- Deciding on dosage
- Monitoring levels and metabolism
Estrogen Therapy

• Measure levels before giving extra estradiol (especially early in menopause)
• **Select the estrogen(s) you wish to use**
• Selection of the carrier and route of administration
• Deciding on dosage
• Monitoring levels and metabolism
Why not give estrone?

- It is an estradiol precursor—so you have to give more to get the same effect
- It is a weaker estrogen—so you have to give more to get the same effect
- It is metabolized differently than estradiol (16OH estrone)
- Metabolism varies from person to person (depending on sulfation and 17βHSD and the detoxification pathways)
ESTRIOL
FDA’s position on estriol:

“The Agency's position has been improperly cast as a ban on estriol. But FDA has repeatedly stated that it respects a healthcare provider's decision that his or her patient should receive estriol.”

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm183078.htm
The Estriol Controversy

• Use of oral E3 in the U.S. largely limited to followers of Jonathan Wright (and their followers)
• Wright measured estrogens in blood samples of premenopausal women and calculated the ratio of E1, E2 and E3. He then attempted to replace to those levels and ratios. Triest failed to create the desired ratios (due to metabolism) and he switched the formula to Biest.
• He and others believe that estriol protects the breast from cancer caused by more potent estrogens when they are given together.
So, I did a little research for you...
There were 91 articles supporting the use of estriol and 44 that did not.
Breast
Lemon HM 1966
Wotiz HH, Shane J, Vigersky R 1966
Lemon HM 1969
Cole P, MacMahon B 1969
Lipsett MB 1971
Hellman L, Zumboff B, Fishman J 1971
Lemon HM 1972
Lemon HM 1973
Rudal G, Apiou F, Muel B 1975
Zumboff B, Fishman J, Bradlow HJ 1975
Lemon HM 1975
xLemon HM 1975
Lemon HM 1975
Lemon HM 1975
Lemon HM 1975
Lemon HM 1975
Lemon HM 1975
Lemon HM 1975
Lemon HM 1975
Gross J, Modan B, Bertini B 1977

Bone
Lindsay R, Hart DM, MacLean A et al. 1979
Nishibe A, Morimoto S, Hirota K et al 1996
Nozaki M, Hashimoto K, Inoue Y et al 1996
Matsuo T, Hiraoka K 1979
Luo H, Liao EV 2003
Terauchi M, Obayashi S, Aso I 2006

Cardiovascular
Baud WE, Finver ML, Milne IG 1957
Zaki K, Sami G, Nour H 1972
Davies T, McNicol GP, Fieldhouse G et al 1975
Toy JL, Davies JA, McNicol GP 1976
Kikuchi N, Urabe M Iwasaki et al 2000
Hellberg D, Nilsson S 1984

Endometrium
Miyake T, Pincus G 1985
Kicovic PM, Cortes-Prieto J, Milovey 2015
Klopper A 1980
Punnoonen R, Soderstrom KO 1983
Monteneri C, Zarbo, G, Garafola A 1987

Estrogenic effect ESTRIOIL w/ ESTRADIOIL
Liberman ME, Maurer RA, Gorski J 1978

Leukemia
Lemon HM 1980
Lemon HM 1980
Clark JH, Markverich BM 1983
Wotiz HH, Beebe DR, Muller E 1984
Lemon HM, Kumar PF, Peterson C, et al. 1980
Bergkvist L, Adamz HP, Persson J et al 1980
Shima N, Kojima S, Kuboera A, Tsuru H 1978
Lyyttinen H, Pukkala E, Ylikorkala O 2006
Rosenberg LU, Magnusson C, Lindstrom E 1981
Esteva R, Nazar, ACP, Baracat 2003
Pfeller G, Glatt C, Konigberg R 2011

Brain
Martius G, Horschler KH 1975
Schiff J, Tulchinsky LB, Ryan JK 1980
Pozzi S, Benedusi V, Maggi A et al 2006
Yonker JE, Abdollahz, Erikkson E et al 2010
Morinaga M, Hirohata M, Ono K et al 2007
Watson CS, Jen YC, Kochakyan MV 2008
Sapovin S, Fedotova IO, Masalova O 2008
Cipolla MJ, Goodeva JIA, Giebman MJ 2009
Gold SM, Sasadhar MV, Morales LB, 2009
Fedotova IO 2010
Morinaga M, Ono K, Takasaki J 2011


Menopause symptoms
Perovic D, Kopatic B, Stankovic T 1975
Borglin NE Staland B 1975
Trinting Yas, Akus MF, Greenblatt RB 1978
Utan WH 1980
Bergink EW, Crohn N, Dahlgren E et al 1981
Gat A, Baraghi F, Barbieri C et al 1982
Lauritsen C 1987
Wren BG 1982
Cheng GI, Liu JL, Zhang Q 1992
Yang TS, Tsai SH, Chang SP 1995
Minaguchi H, Umemura T, Shirasu K 1996.
Mells GB, Cagnacci A, Fruni V et al 1996
Takahashi K, Manabe A, Okada M et al 2000
Hayashi T, Ito K, Hano K et al 2000
Takahashi K, Okada M, Ozaki T et al 2000
Palacios S, Castelo-Branco C, Canelo MJ 2005
Chollet JAT, Carter G, Meyn LA et al 2009
Kika G, Jum S, Mori A 2009
Multiple Sclerosis
Jansson I, Olsson T, Holmdahl R 1994
Kim S, Liva SM, Dalal MA et al 1999
Bebo BF Jr, Fyfe-Johnson A, Adlard K et al 2001
Scotte NL, Liva SM, Klutche R 2002
Zang YC, Halder JB, Hong J 2002
Gold SM, Voekhul RR 2005
Cohens RA 2009
Crawford DK, Mangiardi M, Song B et al 2010
Production/Metabolism/structure/function
Wicks AE 1956
Merrill RC 1958
Brecher PI, Wotiz HH 1967
Zumboff B, Fishman J, Gallagher TF 1968
Anderson JN, Peck EU, Clark JH 1974
Rotti K, Stevens J, Watson D 1975
Persiansin LV, Storchak SV, Bobrovka E 1975
Fishman J, Hellman L 1976

Immune system
Zuckermann SH, Ahmari SE, Bryan-Poole N 1996
Enomoto N, Yamashita S, Schmemper P 1999
Tog H, Farias, E, Zarate AI et al 2008
Egon PK 2010

Nonspecific peritoneum
Zuckerman SH, Ahmari SE, Bryan-Poole N 1996
Enomoto N, Yamashita S, Schmemper P 1999
Zang YC, Halder JB, Hong J 2002
Zang YC, Halder JB, Hong J, Rivera VM et al 2002
Soldan SS, Retouret AIA, Sicotte NL et al 2003
Soldan SS, Alvarez, Retouret AI, 2003
Shishnov SV, Nekrasova IV, Orlova EG 2000
Tiwi-Woodruff S, Voekhul RR 2009

Papenfuss TL, Powell ND, McClain MA 2011
Reviews
Follingstad AH 1978
No authors listed 1979
Diczfalusy E 1984
Peat R 1997
Head KA 1998
Taylor M 2001
Curcio JJ, Smolinski D, Dye J 2005
Speroff L 2005
Curcio JJ, Wollner DA, Schmidt JW et al 2008
Cirigliano M 2007
Fugh-Berman A, Bythrow J 2007
Bennink HJ 2008
Sites CK 2009
Boothby LA, Doering PL 2008
Holtof K 2009
Miller H 2009
Conway E 2011
Skin
Schmidt JB, Spona J 1983
Punnonen R, Baajalainen P, Telsala K 1987
Schmidt JB, Binder M, Macheiner W et al 1995
Gaby AR 2006
Uterus
Hisaw FL, Velardo JR, Goolsby CM 1954
Huggins C, Jensen EV 1955
Lan NC, Katzenellenbogen BS 1976
Martin L, Pollard JW, Fagg B 1976
Bergink EW 1980

Other chemicals
Lemon HM. 1987 RAT
Cheng GJ, Liu JL, 1993
Mukherjee TK, Nathan, Dinh H, et al. 2003-
Crawford DK, Mangiardi M, Song B et al 2010
Prostate
MArmorston J, Lombardo LJ Jr, Myers SM et al 1965
No Abstract
Summary of estriol in various organ systems
Genitourinary: 35 papers

- Huggins C, Jensen EV 1955
- Edgren RA, Calhoun DW 1957
- Merrill RC 1958
- Hustin J. Van den Eynde JP 1977
- Kicovic PM, Cortes-Prieto J, Milojevic S 1980
- Luisi M, Franchi F, Kicovic PM 1980
- Klopper A 1980 REVIEW No real info.
- Trevoux R, van der Velden WH, Popovic D 1982
- Clark JH, Markaverich BM 1983
- Weiderpass E, Baron JA, Adami HO et al 1999
- Punnonen R, Soderstrom KO 1983
- Schwenzer T, Buth C, Degen W et al 1987
- *Kanne B, Jenny J 1991
- van der Linden MC, Gerretsen G, Brandhorst MS 1993
- ERiksen BC, Hunskar S 1991
- Schmidbauer CP. 1992
- Heimer GM, Englund DE. 1992
- Raz R, Stamm WE. 1993
- Whittington R, Faulds D 1994
- Vooijs GP, Geurts TB 1995
- Schar G, Kockli OR, Fritz M et al 1995
- Sitruk-Ware R, Thomas JL 1994
- Lose G, Englev E 2000
- Dugal R, Hesla K, Sordal T et al 2000
- Ozkinay E, Terek MC, Yayci M 2005
- Zullo MA, Plotti F, Calcagno M 2005
- Vahlensieck W, Bauer H. 2006
- Perepanova TS, Khazan PL 2007
- Kobata SA, Girao MJ, Baracat EC 2008
- Davidov MI, Petruniaev AI, Bunova NE. 2009
- Senok AC, Verstraelen H, Temmerman 2009
- Wenderlein M 2010
- Donders GG, Van Bulck B, Van de Walle P et al
- Head KA. 2008
Genitourinary

**Oral**
- Weiderpass E, Baron JA, Adami HO et al 1999-789
- Punnonen R, Soderstrom KO 1983-16
- van der Linden MC, Gerretsen G, Brandhorst MS 1993-62
- Cardozo L, Rekers H, Tapp A et al 1993

**Transvaginal**
- Schar G, Kockli OR, Fritz M et al 1995
- Sitruk-Ware R, Thomas JL 1994-135
- Lose G, Englev E 2000-117
- Ozkinay E, Terek MC, Yayci M 2005-360
- Zullo MA, Plotti F, Calcagno M 2005-28
- Kobata SA, Girao MJ, Baracat EC 2008-41
- Davidov MI, Petruniaev AI, Bunova NE. 2009-51
- Donders GG, Van Bulck B, Van de Walle P et al-46
- Kicovic PM, Cortes-Prieto J, Milojovic S 1980-74
- Luisi M, Franchi F, Kicovic PM 1980-14
- Trevoux R, van der Velden WH, Popovic D 1982-82
- Kanne B, Jenny J 1991 -15
- Schmidbauer CP. 1992-629
- Raz R, Stamm WE. 1993-93

**Meta-analysis**
- Vooijs GP, Geurts TB 1995
My conclusion:

• Estriol, especially when given transvaginally in the appropriate dosing is an excellent and adequately studied therapy for atrophic vaginitis and urogenital symptoms.

• Transvaginal Estriol 0.5mg/Gm
  sig: 1 applicator (1Gm) hs X3 weeks then twice weekly as needed.
Effect of Estriol on Menopausal Symptoms

20 studies
Studies of Estriol in Menopause

• 20 Studies, all in human females
• Combined total of 1938 women studied (only 3 studies had more than 100 participants)
• Control of symptoms 8/9 said “yes”
• Safety of the endometrium 6/6 said “yes”
• Positive GU effects 6/7 said “yes”
• Prevented bone loss 5/6 said “yes”
• Side effects 4/4 said “no”
• Lowered FSH/LH 2/4 said “yes”
• Raised E1 or E2 2/3 said “yes”
Estriol and the Endometrium

• 8 articles, one was a review, one was rabbit study, one a histology study.
• Of the 5 remaining one was a meta-analysis which was done on 12 studies 215 women and was positive.
• Of the remaining 4 studies, one was positive showing no effect on the endometrium and the other three were negative showing some potential to create endometrial hyperplasia or cancer.
• So the verdict was split: 2 positive and three negative with pretty small numbers of women.
• The results were different for oral vs vaginal route with oral more dangerous to the endometrium.
Estriol and the Endometrium - Conclusions

- Trans-vaginal estriol in recommended doses does not require progestogen co-therapy to protect the endometrium
- Oral estriol in usual doses 2mg-8mg needed for symptom relief should be given with a progestogen to protect the endometrium
Estriol and Breast Cancer

37 articles
1. Breast cancer and estriol

- Lemon HM 1966
- Wotiz HH, Shane J, Vigersky R, Brecher PI 1966
- Lemon HM 1969
- Cole P, MacMahon B 1969
- Lipsett MB 1971
- Hellman L, Zumoff B, Fishman J 1971
- Lemon HM 1972
- Lemon HM 1973
- Rudali G, Apiou F, Muel B. 1975
- Zumoff B, Fishman J, Bradlow HL 1975
- Lemon HM 1975
- Lemon HM 1975
- Lemon HM 1975
- Lemon HM 1975
- Zumoff B, Fishman J, Bradlow HL 1975
- Tominaga T, Tei N, Kitamura M 1975
- Deshpande N, Carson P, Horner J 1976
- Gross J, Modan B, Bertini B 1977
- Lemon HM 1977
- Lippman M. Monaco ME, Bolan G 1977
- Wotiz HH, Chatrtora SC, Kudisch M et al. 1978
- Liberman ME, Maurer RA, Gorski J 1978
- Lemon HM 1980
- Lemon HM 1980
- Clark JH, Markaverich BM 1983
- Wotiz HH, Beebe DR, Muller E 1984
- Bergkvist L, Adami HO, Persson I et al 1989
- Shimura N, Kojima S, Kubodera A 1995
- Lyytinen H, Pukkala E, Ylikorkala O 2006
- Rosenberg LU, Magnusson C, Lindstrom E 2006
- Estevao RAF, Nazario ACP, Baracat EC 2007
- Pfeller G, Glatz C, Konigberg R 2011
Eliminate no abstract, no info, or duplicates of the same study
2. Breast cancer and estriol

- Zumoff B, Fishman J, Bradlow HL 1975
- Lemon HM 1975
- Zumoff B, Fishman J, Bradlow HL 1975
- Tominaga T, Tei N, Kitamura M 1975
- Deshpande N, Carson P, Horner J 1976
- Gross J, Modan B, Bertini B 1977
- Lemon HM 1977
- Lippman M. Monaco ME, Bolan G 1977
- Lemon HM 1980
- Lemon HM 1980
- Clark JH, Markaverich BM 1983
- Wotiz HH, Beebe DR, Muller E 1984
- Lemon HM, Kumar PF, Peterson C. 1989
- Bergkvist L, Adami HO, Persson I et al 1989
- Shimura N, Kojima S, Kubodera A 1995
- Lyytinen H, Pukkala E, Ylikorkala O 2006
- Rosenberg LU, Magnusson C, Lindstrom E 2006
- Estevao RAF, Nazario ACP, Baracat EC 2007
- Lappano R, Rosano C, De Marco P. 2010
Eliminate all the non-human studies
3. Breast cancer and estriol

- Zumoff B, Fishman J, Bradlow HL 1975
- Zumoff B, Fishman J, Bradlow HL 1975
- Tominaga T, Tei N, Kitamura M 1975
- Deshpande N, Carson P, Horner J 1976
- Gross J, Modan B, Bertini B 1977
- Lemon HM 1980
- Clark JH, Markaverich BM 1983

- Bergkvist L, Adami HO, Persson I et al 1989
- Lyytinen H, Pukkala E, Ylikorkala O 2006
- Rosenberg LU, Magnusson C, Lindstrom E 2006
- Estevao RAF, Nazario ACP, Baracat EC 2007
Eliminate the reviews and opinion pieces and the studies just documenting hormone levels.
Eliminate the reviews and opinion pieces and the studies just documenting hormone levels.
4. Breast cancer and estriol

- Tominaga T, Tei N, Kitamura M 1975
- Deshpande N, Carson P, Horner J 1976
- Gross J, Modan B, Bertini B 1977
- Bergkvist L, Adami HO, Persson I et al 1989
- Lyytinen H, Pukkala E, Ylikorkala O 2006
- Rosenberg LU, Magnusson C, Lindstrom E 2006
- Estevao RAF, Nazario ACP, Baracat EC 2007
5. Breast cancer and estriol

• Bergkvist L, Adami HO, Persson I et al 1989
• Lyytinen H, Pukkala E, Ylikorkala O 2006
• Rosenberg LU, Magnusson C, Lindstrom E 2006
6. Breast cancer and estriol

Bergkvist L, Adami HO, Persson I et al. 1989 HUMAN 23,244 women on estrogen or estrogen/progestin. 22% used estriol. Estradiol increased risk RR 1.7 after nine years. Estriol did not... but then neither did CEE. POSITIVE

Lundstrom E, Wisczek B, von Palffy Z, Soderqvist G et al. 2001 HUMAN 158 women 51 of whom were using 2mg estriol. An increase in mammographic density was much more common among women taking continuous combined HRT (40%) than for those using oral low-dose estrogen (6%) and transdermal (2%) treatment. (compared to transdermal estradiol) POSITIVE/ but NEGATIVE compared with transdermal E2

Lyytinen H, Pukkala E, Ylikorkala O. 2006 HUMAN prospective observational study of Finnish registry showed oral Estradiol (especially more than 1.9mg/day and transdermal estradiol were associated with increased risk (although the transdermal estradiol was not dose related which says something is off here) Oral estriol (7,941 women) did not increase the risk nor did vaginal estrogens POSITIVE

Rosenberg LU, Magnusson C, Lindstrom E. 2006 HUMAN population based case control study in Sweden. Looking at type of HRT and breast cancer histology. Low potency estrogen (mostly estriol) appeared to be associated with an increased risk of lobular cancer but the association was strongest for short term use. NEGATIVE
The Theory

• Estriol has breast protective properties as was seen in rat studies where estriol protected rats from developing breast cancers after exposure to a carcinogen.

• Estriol, during pregnancy, protects the mother from the high levels of estradiol and other more potent estrogens (progesterone is a confounder).

But what do we know about estriol by itself or in combination with estradiol?
Estriol Protects the Breast from Stronger Estrogens

- Clark JH, Paszko Z, Peck EJ Jr. 1977
- Schiff I, Wentworth B, Koos B, Ryan KJ, Tulchinsky D 1978
- Sipinen S. 1979
- Clark JH, Hardin JW, McCormack SA 1979
- Ottosson UB, Carlstrom K, Johansson BG et al 1984
- Muller RE, Traish AM, Wotiz HH 1985
- Melamed M, Castano E, Notides AC et al 1997
Estriol Protects the Breast from Stronger Estrogens

• Clark JH, Paszko Z, Peck EJ Jr. 1977
• Sipinen S. 1979
• Clark JH, Hardin JW, McCormack SA 1979
• Ottosson UB, Carlstrom K, Johansson BG et al 1984
• Muller RE, Traish AM, Wotiz HH 1985
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- Melamed M, Castano E, Notides AC et al 1997: “The effects were maximal at 10 fold molar excess but were dose dependent Max=decreased E2 transcription by 85% although E2 binding only decreased by 50%”
6. Breast cancer and estriol

Bergkvist L, Adami HO, Persson I et al. 1989 HUMAN 23,244 women on estrogen or estrogen/progestin. 22% used estriol. Estradiol increased risk RR 1.7 after nine years. Estriol did not... but then neither did CEE. POSITIVE

Lundstrom E, Wisczek B, von Palffy Z, Soderqvist G et al. 2001 HUMAN 158 women 51 of whom were using 2mg estriol. An increase in mammographic density was much more common among women taking continuous combined HRT (40%) than for those using oral low-dose estrogen (6%) and transdermal (2%) treatment. (compared to transdermal estradiol) POSITIVE/ but NEGATIVE compared with transdermal E2

Lyytinen H, Pukkala E, Ylikorkala O. 2006 HUMAN prospective observational study of Finnish registry showed oral Estradiol (especially more than 1.9mg/day and transdermal estradiol were associated with increased risk (although the transdermal estradiol was not dose related which says something is off here) Oral estriol (7,941 women) did not increase the risk nor did vaginal estrogens POSITIVE

Rosenberg LU, Magnusson C, Lindstrom E. 2006 HUMAN population based case control study in Sweden. Looking at type of HRT and breast cancer histology. Low potency estrogen (mostly estriol) appeared to be associate with an increased risk of lobular cancer but the association was strongest for short term use. NEGATIVE
My conclusion about Estriol

- There is very little evidence to support the theory that Estriol in combination with other estrogens modifies the risk of breast cancer.
- Estriol by itself has some potential as hormone therapy, but is not as effective as estradiol 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.
- The combination of estriol with other estrogens like estradiol by mouth may act as a competitive inhibitor of the positive effects of estradiol 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 estriol (2mg or more) may not be enough to block estradiol and is enough to stimulate the endometrium requiring a progestogen.
- Estriol vaginal cream or suppositories have significant research to support their use. The vagina reacts differently than other tissues to estriol and vaginal estriol in these doses does not require a progestogen to protect the endometrium.
Estrogen Therapy

• Measure levels before giving extra estradiol (especially early in menopause)
• Select the estrogen(s) you wish to use
• Selection of the carrier and route of administration
• Deciding on dosage
• Monitoring levels and metabolism
Route of delivery

Overwhelming evidence suggests that transdermal and perhaps trans-vaginal estradiol is superior to oral administration even when giving micronized estradiol rather than CEE.
Citations for previous slide: “Route of Delivery”


Estradiol

• Patch and gel give adequate blood levels and can be measured in blood and urine
• Creams have a different profile of absorption and create higher levels in saliva, which may represent tissue levels (not proven) but lower levels in blood bring into question the use of either when measuring the result of creams
• The smaller the area of skin covered (with adequate absorption) the less depot-ing in fat.
Rhythm of Estradiol

• Estradiol levels are normally rhythmic
• Estradiol (ERα) is involved with regulation of “clock genes” in breast cancer\textsuperscript{1,2,3,4}
• Application in the AM mimics this rhythm
• Use of creams creates a depot effect
• Use of constantly eluting patches and vaginal rings does not allow and may block these effects

Circadian Rhythms of Estradiol and Hot Flashes
Estrogen Therapy

- Measure levels before giving extra estradiol (especially early in menopause)
- Select the estrogen(s) you wish to use
- Selection of the carrier and route of administration
- Deciding on dosage
- Monitoring levels and metabolism
Best Practice

• Start *low* and work up slowly
• Estrogen symptoms are the only ones that are sensitive enough to use to titer HRT
• If you tie all your hormones together you can use symptoms to target ideal hormone levels
• Treat to a level of minimal hot flashes and NO breast tenderness
• Then repeat hormone levels.
<table>
<thead>
<tr>
<th>Body as a Whole</th>
<th>21%</th>
<th>39%</th>
<th>37%</th>
<th>29%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>5%</td>
<td>18%</td>
<td>13%</td>
<td>10%</td>
</tr>
<tr>
<td>Pain</td>
<td>1%</td>
<td>8%</td>
<td>11%</td>
<td>7%</td>
</tr>
<tr>
<td>Back Pain</td>
<td>4%</td>
<td>8%</td>
<td>9%</td>
<td>6%</td>
</tr>
<tr>
<td>Edema</td>
<td>0.5%</td>
<td>13%</td>
<td>10%</td>
<td>6%</td>
</tr>
<tr>
<td>Gastro-Intestinal</td>
<td>9%</td>
<td>21%</td>
<td>29%</td>
<td>18%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>0.0%</td>
<td>11%</td>
<td>16%</td>
<td>8%</td>
</tr>
<tr>
<td>Nausea</td>
<td>1%</td>
<td>5%</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Flatulence</td>
<td>1%</td>
<td>3%</td>
<td>7%</td>
<td>1%</td>
</tr>
<tr>
<td>Musculo-Skeletal</td>
<td>7%</td>
<td>9%</td>
<td>11%</td>
<td>4%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1%</td>
<td>5%</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>13%</td>
<td>10%</td>
<td>11%</td>
<td>1%</td>
</tr>
<tr>
<td>Depression</td>
<td>1%</td>
<td>5%</td>
<td>8%</td>
<td>0%</td>
</tr>
<tr>
<td>Reproductive</td>
<td>12%</td>
<td>18%</td>
<td>41%</td>
<td>11%</td>
</tr>
<tr>
<td>Breast Pain</td>
<td>5%</td>
<td>8%</td>
<td>29%</td>
<td>4%</td>
</tr>
<tr>
<td>Leukorrhea</td>
<td>1%</td>
<td>6%</td>
<td>7%</td>
<td>1%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>15%</td>
<td>26%</td>
<td>29%</td>
<td>14%</td>
</tr>
<tr>
<td>URTI</td>
<td>6%</td>
<td>17%</td>
<td>17%</td>
<td>8%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>0.5%</td>
<td>3%</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>4%</td>
<td>4%</td>
<td>5%</td>
<td>3%</td>
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<tr>
<td>Rhinitis</td>
<td>2%</td>
<td>4%</td>
<td>6%</td>
<td>1%</td>
</tr>
<tr>
<td>Skin and Appendages</td>
<td>19%</td>
<td>12%</td>
<td>12%</td>
<td>15%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0.5%</td>
<td>6%</td>
<td>3%</td>
<td>6%</td>
</tr>
</tbody>
</table>
Dosing Estradiol

- It doesn’t matter how much you give, it matters how much you get!
- Dosing should not be “one sized fits all” but rather titrated to minimal effective dose.
- This can be done with patch (by cutting it down) by cream or by gel (although measurements are crude for all three at this time)
Estrogen Therapy

• Measure levels before giving extra estradiol (especially early in menopause)
• Select the estrogen(s) you wish to use
• Selection of the carrier and route of administration
• Deciding on dosage
• Monitoring levels and metabolism
My conclusions about estrogen

• Estradiol is the best estrogen to use because it can be given in small doses and it can be measured.
• Estradiol should be given transdermally in the smallest amount possible. Gel allows us to pulse estradiol, which is physiologic.
• Estriol is very effective and safe when used transvaginally for vaginal and urogenital symptoms. While it may not protect the breast in the doses usually used, it is unlikely to be dangerous.
Progesterone
There is overwhelming evidence to say that progestins, although more anti-proliferative in the endometrium, are not safe or effective in other important tissues.
Estrogen Only Rx

Unopposed Estrogen and Cancer

Ian H. Thorneycroft, PhD, MD

The relationship between estrogen use and gynecologic and other cancers has been controversial for many years and will probably remain so because of the methodologic challenges in conducting studies in this area and the difficulty of applying epidemiologic data to individual patients. A risk-benefit ratio, no matter how rigorously calculated, is still a theoretical construct. In spite of a starting point, however, for the decisions that must be made by individual patients and their physicians concerning the use of hormone therapy (HT). This article reviews the data on cancer and unopposed estrogen therapy (ET) with attention to methodologic aspects of the research that enter into its interpretation. In the area of cancer specifically, it is important to review all of the literature, not just the results of certain individual studies and studies in certain journals. As accurately as we can, risk and benefit. As the first ET study failed to show "No single study has a monopoly on the truth." For discussion, I place more emphasis on my opinion on the results of meta-analysis and whole literature review rather than individual articles. The reader must be aware of the selection process of articles to be included in a meta-analysis, however. DeMent and Page's computed an increased breast cancer risk with estrogen, yet Semburg and colleagues reported an increased risk. Both articles were published in 1991, but the former covered 27 studies and the latter 16.

ENDOMETRIAL CANCER

This risk emerged

The Female Patient Supp February 2004 pg 19
Is (bioidentical) progesterone safe enough to use short- or long-term or should we try to avoid it (such as in women without a uterus) and how do we give it and how much?
The difficulty studying progesterone

Confusing the terminology
The use of the term “Progesterone” when “Progestins” are actually used:

• Faludi AA et al. (2004) Progesterone abolishes estrogen and/or atorvastatin endothelium dependent vasodilatory effects. Atherosclerosis 177: 89–96—Used E2 and Norethisterone

• Schulman SP et al. (2002) Effects of acute hormone therapy on recurrent ischemia in postmenopausal women with unstable angina. J Am Coll Cardiol 39: 231–237. “0.86 for estrogen plus progesterone”—Used CEE plus MPA

• Popp AW et al. (2006) Prevention of postmenopausal bone loss with long-cycle hormone replacement therapy. Maturitas 53: 191–200 “which triggered renewed interest in long-cycle HRT regimens (estrogen replacement therapy with progesterone-free intervals up to 6 months)”—Used E2 plus Norethisterone
Progesterone is complicated...

- Progesterone receptors need estradiol stimulation to be present in tissue.
- Progesterone receptors PRα and PRβ have different transcriptional activities; PRα controls PRβ, which appears to do all the work.
- PRα is up-regulated in breast cancer cells and PRβ is down regulated in cancer cells.
- Progesterone effect on cell cycle is complex.
- Progesterone metabolites 5αOH and 3αOH have different effects on cell growth and on GABA receptors in the brain.
Progesterone in a cell model that doesn’t require estrogen for PR presence (T47D-YB) showed that progesterone drives cells through one cell growth cycle and then arrests it in late G1.
Effect of Progesterone on Breast Mitosis

Fig. 4. The biphasic action of progesterone on breast cells, deduced from Grushong et al.\textsuperscript{24}.

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Br J Obstet Gynaecol 106, 1006–1018
Hypothesis: Progesterone Primed Breast Cancer Cells for Cross-Talk with Proliferative or Antiproliferative Signals

Carol A. Lange, Jennifer K. Richer, and Kathryn B. Horwitz

University of Colorado Health Sciences Center
Department of Medicine
Division of Endocrinology
Denver, Colorado 80262

INTRODUCTION

The effects of progesterone in the breast are complex and due to the ability of the weak estrogen and progesterone model system, the progesterone, progestins, and antiprogesterone in combination with steroids in this process. We propose a role for progesterone in LANGE CA Molecular Endocrinology 1999;13(6):829 the role of steroid hormones to growth driven primarily by peptide growth factors.

...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
Progesterone
What this means...

- This could mean that giving progesterone cyclically (sequentially) after menopause, especially if there is enough estrogen around to upregulate progesterone receptors would repeatedly cycle breast cells through division with it’s attendant risks of gene disruption and cancer. (In these cell studies it took just 72 hours for the cells to become sensitive to progesterone again and go through another cell cycle.)

- When estrogen levels are low PR levels are concomitantly low confounding how this works in real life. Since the growth arrest requires PR the level of estrogen (which induces PR) is critical to whether breast cells get a growth promoting or growth inhibiting signal from progesterone.

- We need to know more about how EGR and other growth signals (ER) interact with this progesterone mediated pause in G1
SEEMS

- Hormones, chemicals, drugs that up or down regulate 17βHSD’s, STS, SULT, 3βHSD or aromatase thereby making estradiol more or less available to this tissue.
- Progestins are known SEEMS which negative effects that may explain their cancer causing effect on the breast.
- Progesterone has not been as well studied and it’s effects on the estrogen enzymes is controversial.
Concerns:

• Progesterone has anti-androgenic effects-if testosterone is anti-proliferative in the breast progesterone may block this effect$^{1,2,3}$
• Alternatively, since progesterone metabolites block 5α-reductase they may raise the levels of testosterone.$^4$
• Progesterone metabolites have different effects so metabolizing enzymes could be important
Citations for “Concerns”


Is there such a thing as a “progesterone deficit”?

These studies on rhesus monkeys suggest that the cardiovascular system suffers deficit of progesterone after menopause (especially in women who are under stress)\(^1,2,3\)

Progesterone pre and post menopause

• Women who had their cancers removed in the luteal phase lived longer\(^1\)
• Infertility patients with low progesterone had more breast cancers (may also have been insulin resistant however)\(^2\)
• E3N shows that early and late menopause patients show a different effect of estrogen and progesterone on breast cancer. (This means that the effect of progesterone is likely to be determined by the LEVEL of estrogen.)\(^3\)
Citations for previous slide: “Progesterone pre and post menopause”


What do we know?

• Man-made progestins have many negative side effects in the brain, breast and cardiovascular system.
• Progesterone is usually better tolerated, may be safer but the only RCT (PEPI Trial) did not look at end points only intermediate markers of disease and it showed the worst profile in terms of breast symptoms in the women on progesterone.
• When estrogen levels are high (pre-menopause) cycling progesterone induces growth while continuous progesterone induces differentiation (pregnancy).
• In early menopause progesterone continuously may protect the breast but in later menopause when there are no progesterone receptors progesterone may have different effects.
## 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 assignment† and symptom group</th>
<th>Comparison group‡§</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td>Breast discomfort</td>
<td></td>
</tr>
<tr>
<td>CEE</td>
<td>1.16 (0.70, 1.93)</td>
</tr>
<tr>
<td>CEE + MPA (cyc)</td>
<td>2.27 (1.30, 3.56)</td>
</tr>
<tr>
<td>CEE + MPA (con)</td>
<td></td>
</tr>
<tr>
<td>CEE + MP</td>
<td></td>
</tr>
<tr>
<td>Perceived weight gain</td>
<td></td>
</tr>
<tr>
<td>CEE</td>
<td>0.80 (0.54, 1.19)</td>
</tr>
<tr>
<td>CEE + MPA (cyc)</td>
<td>0.69 (0.47, 1.03)</td>
</tr>
<tr>
<td>CEE + MPA (con)</td>
<td>0.61 (0.41, 0.91)</td>
</tr>
<tr>
<td>CEE + MP</td>
<td>0.87 (0.60, 1.26)</td>
</tr>
<tr>
<td>Perceived weight loss</td>
<td></td>
</tr>
<tr>
<td>CEE</td>
<td>1.22 (0.61, 2.46)</td>
</tr>
<tr>
<td>CEE + MPA (cyc)</td>
<td>1.52 (0.78, 2.97)</td>
</tr>
<tr>
<td>CEE + MPA (con)</td>
<td>1.85 (0.97, 3.56)</td>
</tr>
<tr>
<td>CEE + MP</td>
<td>2.22 (1.17, 4.30)</td>
</tr>
</tbody>
</table>

* Odds ratios are adjusted for baseline symptom level, clinical site, and uterus status.
† 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).
‡ Entries in table are odds ratios with 95% confidence intervals from generalized Wald tests in parentheses.
§ 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&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Relative risk&lt;sup&gt;b&lt;/sup&gt; (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>766/244,632</td>
<td></td>
</tr>
<tr>
<td>Estrogen alone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td>79/20,347</td>
<td>1.29 (1.02–1.65)</td>
</tr>
<tr>
<td>[2–4]</td>
<td>24/6,747</td>
<td>1.26 (0.83–1.99)</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>p for trend</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>Estrogen + progesterone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td>129/40,537</td>
<td>1.00 (0.83–1.22)</td>
</tr>
<tr>
<td>[2–4]</td>
<td>18/8,867</td>
<td>0.71 (0.44–1.14)</td>
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<tr>
<td>[4–6]</td>
<td>33/11,647</td>
<td>0.95 (0.67–1.36)</td>
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<tr>
<td>6+</td>
<td>30/7,519</td>
<td>1.25 (0.87–1.82)</td>
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<tr>
<td>p for trend</td>
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<tr>
<td>Estrogen + dydrogesterone</td>
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<tr>
<td>&lt;2</td>
<td>108/31,045</td>
<td>1.15 (0.94–1.43)</td>
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<td>[2–4]</td>
<td>16/6,923</td>
<td>0.84 (0.51–1.38)</td>
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<tr>
<td>[4–6]</td>
<td>28/8,697</td>
<td>1.15 (0.79–1.71)</td>
</tr>
<tr>
<td>6+</td>
<td>21/5,560</td>
<td>1.23 (0.83–1.99)</td>
</tr>
<tr>
<td>p for trend</td>
<td>0.16</td>
<td></td>
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<tr>
<td>Estrogen + other progestagens</td>
<td></td>
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</tr>
<tr>
<td>&lt;2</td>
<td>527/104,243</td>
<td>1.69 (1.50–1.91)</td>
</tr>
<tr>
<td>[2–4]</td>
<td>66/22,792</td>
<td>1.36 (1.07–1.72)</td>
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<td>[4–6]</td>
<td>134/30,189</td>
<td>1.59 (1.30–1.94)</td>
</tr>
<tr>
<td>6+</td>
<td>106/19,942</td>
<td>1.79 (1.44–2.23)</td>
</tr>
<tr>
<td>p for trend</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Weak estrogens&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others&lt;sup&gt;2&lt;/sup&gt;/unknown HRT</td>
<td>56/17,091</td>
<td>0.90 (0.68–1.18)</td>
</tr>
<tr>
<td>Mixed&lt;sup&gt;e&lt;/sup&gt;</td>
<td>82/21,071</td>
<td>1.27 (1.01–1.60)</td>
</tr>
<tr>
<td></td>
<td>538/130,594</td>
<td>1.25 (1.11–1.41)</td>
</tr>
</tbody>
</table>
Progesterone- routes of delivery

- Transdermal gel
- Transdermal cream
- Oral micronized
- Vaginal gel
- Vaginal ring (available in South America)
Progesterone dosing
My Conclusions:

• Progesterone is the most complex of the three female hormones. It affects both estrogen and testosterone signaling as well as peptide growth factors and providing the precursors for cortisol.

• Progesterone is safe and useful during the pre- and peri-menopausal period to treat the imbalance between estrogen and progesterone. After menopause estradiol is required for progesterone to work through it’s receptors although it may still function via transmembrane receptors.

• After menopause progesterone could potentiate the negative effect of peptide growth factors on the breast. After menopause the safety of progesterone is probably determined by the levels of estradiol and the presence of peptide growth factors.

• Progesterone can be used as a GABAergic drug for anxiety and sleep.

• There is still inadequate data on Progesterone…it’s just better than the man-made alternatives.
Testosterone
Should women receive testosterone and if so what form and what route?
Androgens predominantly show antiproliferative effects in breast carcinoma cells, but association between AR status and the clinical outcome of the patient remains controversial, perhaps partly because AR status does not necessarily reflect androgenic action in breast carcinoma.
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(trend) = .041).
Evidence of anti-proliferative effect of testosterone

• “Androgen receptors are found in virtually every tissue in women as well as men, including breast, bone and brain, indicating that androgens and their metabolites may play an important role in normal tissue homeostasis and possibly in pathologies like breast cancer, osteoporosis, libido and cognitive decline.”

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

• At menarche high levels of testosterone (such as when due to adrenal hyperplasia) inhibit breast development while low levels of testosterone (due to overexpression of CYP3A4) cause premature breast development.

• Androgen receptor blockage causes gynecomastia in men.

• Interactions between progesterone and testosterone (both are metabolized by CYP3A4) are significant (see progesterone)
Testosterone

• Ideal range in menopause .25-.4 ng/mL
• Can be used to modulate SHBG and therefore estrogen
• Not a cause of loss of libido in women as often as we would like to think, although the balance between estrogen and progesterone is important.
• Can increase the risk of breast cancer, however this may depend on its effect on SHGB and its association with insulin resistance.
DHEA

- Oral-doses in women should be MUCH smaller (usually under 10mg although total production is reported as 11-30mg/24 hours)
- Best practice: improve adrenal function and wean off DHEA
- DHEA vaginal cream-new therapy which appears highly effective in vagina but no data is as yet available on tissue levels, effect on estradiol and testosterone or distant effects.
DHEA

• Epidemiological studies show correlations between high DHEA and breast cancer in post- but not in pre-menopausal women.
• Prolonged high DHEA causes increased IGF-1
• Risk of DHEA is increased in abdominal obesity

Cardiovascular disease
Osteoporosis
Estrogen effect on the brain
Endocrine disruptors

The high degree to which human physiology has endowed peripheral tissue the ability to make it’s own steroids may also make that tissue more susceptible to the effects of endocrine disruptors from the environment. Each tissue in a sense reads it’s own need for estrogen and androgen making it locally with enzymes that can be affected by chemicals from the environment.
My conclusions:

• Large numbers of women are either without ovarian hormones or have greatly diminished ovarian function due to hysterectomy or autoimmunity.

• These women are likely testosterone deficient and may be deficient in other steroid hormone precursors such as progesterone, DHEA and androstenedione.

• These women require replacement to normal levels for age to be optimally healthy and some will require replacement for the rest of their lives.
My conclusions...

• Estradiol is the best estrogen to use as it is effective in very small doses and can be given transdermally but should be monitored using the appropriate laboratory testing.

• There is inadequate evidence to convince me that estriol is useful or important to give in combination although used vaginally is very helpful and safe.

• Pre-menopausal progesterone given cyclically decreases breast cancer risk, balances estrogen/progesterone, is particularly important during perimenopause and, given cyclically, does not increase insulin resistance.
My conclusions...

• Progesterone given continuously (OCP’s) before menopause, increases insulin resistance in high doses. Watch fasting insulin levels.
• Postmenopausally, progesterone may increase the risk of breast cancer in some women, but decreases the risk of endometrial cancer. It should be given continuously.
• When estrogen is given to normalize postmenopausal levels and adrenal function is normal, minimal (no?) progesterone is needed.
• E/P balance is important in the brain, even after menopause.
My conclusions..

- Testosterone is often necessary to lower SHBG allowing lower dosing of estradiol. It is sometimes helpful in women with low libido provided estradiol is normalized.

- DHEA may turn out to be a good hormone replacement option but there is not enough data or dosing or long term effects. In low doses (<10mg) for short periods of time.
TESTING
"Your test results came back. You don’t test well."
Laboratory testing

Who to test?
When to test?
What to test?
Should we measure hormone levels?
In what body fluid and when?
Problems Finding “Normal”

- Hormone levels fluctuate
- Most studies don’t measure hormone levels
- Studies of normal hormone levels are older studies, methodology was unreliable.
- Studies often average incompatible groups
- Reference ranges: What are you really getting?
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
• 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)
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
Serum Testing

“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”

When to Test? - Premenopausal
When to Test:

- Early AM testing is the time of highest hormone for most of the gonadal hormones.
- Probably best to be fasting for consistency between specimens.
- Be sure to have patients record first day of NEXT period so you know what day you did their testing.
Remember:

Circulating levels of estradiol in men and in postmenopausal women do not drive estrogen levels in tissue because estrogen is made locally. Estradiol and estrone in serum reflect rather than direct estrogen action in tissue.

Benefits of Blood Testing

• Newer techniques highly accurate down to very low levels but few labs are actually using these techniques
• Many studies in the literature
• You can measure estrogen metabolites (2/16OH ratios and levels), but not progesterone metabolites
• You can measure SHBG
• It is usually covered by insurance
Problems with Blood Testing

• THERE ARE MANY!
• Newer methods GC or LC-MS/MS are more accurate but not yet available.
• Lab reference ranges are not standardized and can be misleading
• Free testosterone in women is difficult to measure and often calculated rather than measured.\(^1,4\)
Problems with Blood Testing

- Lack of standardization of high-quality steroid hormone assays is a major deficiency in studies. In postmenopausal women, reported levels of serum E$_2$ are highly variable and median normal values differ by approximately a 6-fold factor$^3$.
- Comparison between labs is unreliable
- Levels are affected by time of day and fasting status.
- Hormone levels in women taking transdermal and trans-vaginal hormones may be falsely low in blood compared to tissue$^5$. 
Citations for previous 2 slides: “Problems with Blood Testing”


5. Personal communication with Patrick Hanaway, Genova Labs.
“Estradiol levels tend to fluctuate dramatically during the perimenopausal transition. There is significant overlap of the expected range in menopausal women with values observed during normal menstrual cycles. Estradiol results obtained with different assay methods cannot be used interchangeably in serial testing. To monitor a patient's serial results, it is best to ensure that the same methodology is used each time the test is performed.”

LabCorp
<table>
<thead>
<tr>
<th>Hormone</th>
<th>Production mg/day</th>
<th>Serum level ng/mL</th>
<th>% un-bound</th>
<th>Free level</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHEA-S</td>
<td>6.7 [4.3-12.6]</td>
<td>3-8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Androstenedione</td>
<td>2.8 [1.4-6.2]</td>
<td>0.7-3.0</td>
<td>7.54</td>
<td>.053-.23</td>
</tr>
<tr>
<td>Testosterone</td>
<td>0.3 [.1-.4]</td>
<td>0.2-0.7</td>
<td>1.36</td>
<td>.003-.01</td>
</tr>
<tr>
<td>DHT</td>
<td>0.04 [.02-.05]</td>
<td>0.06-0.14</td>
<td>0.47</td>
<td>.0003-.0007</td>
</tr>
<tr>
<td>Estrone (follicular)</td>
<td>0.11 [.044-.22]</td>
<td>.05 [.02-.1]</td>
<td>3.58 (av)</td>
<td>.0018</td>
</tr>
<tr>
<td>Estrone (mid-cycle)</td>
<td>0.320 [.16-.66]</td>
<td>.125 [.075-.3]</td>
<td></td>
<td>.0045</td>
</tr>
<tr>
<td>Estrone (luteal)</td>
<td>0.16 [.088-.33]</td>
<td>.07 [.04-.15]</td>
<td></td>
<td>.0025</td>
</tr>
<tr>
<td>Estrone (Menopausal)</td>
<td>.048</td>
<td>.04 [.015-.055]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estradiol (follicular)</td>
<td>0.065 [.026-.130]</td>
<td>.065 [.02-.1]</td>
<td>1.81 (av)</td>
<td>.0012</td>
</tr>
<tr>
<td>Estradiol (mid-cycle)</td>
<td>0.321 [.2-.78]</td>
<td>.25 [.150-.6]</td>
<td></td>
<td>.0045</td>
</tr>
<tr>
<td>Estradiol (luteal)</td>
<td>0.160 [.1-.39]</td>
<td>.125 [.073-.3]</td>
<td></td>
<td>.0023</td>
</tr>
<tr>
<td>Estradiol (Menopausal)</td>
<td>.013</td>
<td>.015 [.005-.03]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estriol (Pre-menopausal)</td>
<td>.014-.023</td>
<td>.007-.011</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Salivary Testing
Steroid hormones are transferred into saliva based upon how lipophilic they are and are thought to diffuse across the acinar cells into the saliva.
Salivary glands are not unisex organs!
Benefits of Salivary Testing

• Non-invasive, stress free
• Easily collected specimens circumvent hormonal fluctuations if done multiple times\(^1\)
• Convenient for patient and practitioner (does not need centrifugation or refrigeration)\(^2\)
• Hormones stable in saliva for long periods of time, except mucins in saliva can cause spurious results\(^2\)
• Is preferable to use urine as a noninvasive alternative for steroid determinations because hormones are not converted to water-soluble metabolites

Problems with Salivary Hormone Testing

• Lack of literature standards
• No proficiency testing (CAP, AAB) that reflects saliva hormone levels (CLIA only tests for accuracy and reproducibility with serum)\(^3\)
• Estrogen metabolites not available.
Problems with Salivary hormone testing

• Free hormone enters saliva by diffusion and is not dependent on saliva flow rates but is dependent on the degree of lipophilia P>E2>T. Conjugated hormones, thyroxin and protein hormones enter via ultra-filtration through tight junctions and are highly flow rate dependent therefore not appropriate for salivary testing.¹,²

• Some hormones are metabolized in the gland⁶

• 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 assays³) Some labs concentrate the saliva to obtain measurable levels of hormone and then “calculate” the levels in the original sample.

• Rapid fluctuations in levels¹ May necessitate multiple samples for accuracy.
Problems with Salivary Hormone Testing

- Easily contaminated by food, drugs and hormones on the patient’s hands
- Contamination by blood can dramatically raise hormone levels (gum disease or tooth brushing before collection)
- Hormones that depot in fat produce levels that do not change as fast with dose adjustment- you have to wait longer to retest.
- Cannot be used with sublingual or buccal hormone administration.
- Sialogogues like gum can affect results, other collection devices (Salivette, blood spot paper, foam tip applicator) also affect % recovery of hormone with glucocorticoids>androgens
Citations for previous three slides: “Problems with Salivary Hormone Testing”

Saliva-What does it tell you

- Unbound (active) hormone
- Is thought (by some) to reflect tissue levels
- Hormone levels after transdermal therapy are much higher than plasma: The progesterone conundrum
The Progesterone Conundrum

When measuring *endogenous* progesterone, saliva appears to be a reliable reflection of blood levels. Following progesterone cream dosing, extraordinarily high levels of progesterone are seen in saliva.
The Progesterone Conundrum

Potential explanations:

1. Transdermal progesterone is metabolized by 5α-reductase in the skin.
   Women treated with dutasteride (a 5-α reductase inhibitor) showed insignificantly higher progesterone levels but saliva was still many times higher.\(^1\) However, a rat study showed higher tissue levels in uterus and lung than serum.\(^2\)

2. Progesterone is rapidly absorbed by RBC membranes\(^3\) and delivered to tissues including salivary glands.
   Lewis\(^4\) et. al. did not find high levels in RBC while levels in saliva were very high and variable in 24 postmenopausal women given 20 or 40 mg BID transdermal cream.
   The study cited showed 80% of hormone discarded with RBC while salivary levels are 1-5% of serum and this should be the case before hormone administration as well as after.
Citations for previous slides: “The Progesterone Conundrum”


4. Lewis JG, McGill H, Patton VM, Elder PA. *Caution on the use of saliva measurements to monitor absorption of progeesterone from transdermal creams in postmenopausal women.*
The mechanism by which the serum progesterone levels remain low is not known. However, one explanation is that after absorption through the skin, the lipophilic ingredients of creams, including progesterone, may have a preference for saturating the fatty layer below the dermis. Because there appears to be rapid uptake and release of steroids by red blood cells passing through capillaries, these cells may play an important role in transporting progesterone to salivary glands and other tissues. In contrast to progesterone creams, progesterone gels are water-soluble and appear to enter the microcirculation rapidly, thus giving rise to elevated serum progesterone levels with progesterone doses comparable to those used in creams.

Human erythrocyte membrane. Uptake of progesterone and chemical alterations.

Devenuto F, Ligon DF, Friedrichsen DH, Wilson HL.

PMID: 5349618 [PubMed - indexed for MEDLINE]

MeSH Terms: Substances

LinkOut - more resources
There were small increases in plasma progesterone levels and pregnanediol-3-glucuronide excretion compared to the placebo group and red cell progesterone levels never exceeded plasma levels during progesterone cream use. Saliva progesterone levels were very high and variable in the progesterone cream groups compared to the placebo group and presented a paradox to the usual relationship observed between plasma and saliva progesterone in premenopausal women.
Whether serum or salivary concentrations in the two population groups better reflect availability of P to the tissues is an unresolved question.
Levels of progesterone increased and levels of estradiol decreased in saliva after micro injury.
Chewing gum significantly decreased production time for the second saliva samples by 3-6 min, and had very large effects on assay results, leading to lower IgA and higher T and E in men and women.
Does progesterone reflect tissue levels?

The ultimate question becomes: why does the RBC transfer its load of hormone to the salivary gland cell but not to the endometrial cell in sufficient amounts to produce secretory effects? And if this mechanism is correct, 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?
## Salivary Hormone Normal

<table>
<thead>
<tr>
<th>Hormone</th>
<th>mid-follicular</th>
<th>ovulation</th>
<th>luteal</th>
<th>menopause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol</td>
<td>2.2-4.1pg/ml¹</td>
<td>5.5pg/ml¹</td>
<td>2.7-4.4 pg/m.¹</td>
<td>&lt;dl</td>
</tr>
<tr>
<td>Estrone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estriol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progesterone</td>
<td>27pg/L¹</td>
<td></td>
<td>102pg/L¹</td>
<td></td>
</tr>
<tr>
<td>Testosterone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Lipson SF, Ellison PT. **Comparison of salivary steroid profiles in naturally occurring conception and non-conception cycles.** Human reproduction 1996:11(10):2090-2096.L
## Progesterone levels

<table>
<thead>
<tr>
<th>Lab</th>
<th>Follicular</th>
<th>Luteal</th>
<th>Men.</th>
<th>Oral HT</th>
<th>Transdermal HT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genova</td>
<td></td>
<td></td>
<td>163-669pmol/L</td>
<td>51-210pg/mL</td>
<td></td>
</tr>
<tr>
<td>ZRT</td>
<td>25-100pg/ml</td>
<td>100-600pg/ml</td>
<td>100-1000pg/mL</td>
<td>500-3000pg/ml</td>
<td></td>
</tr>
<tr>
<td>Rocky Mtn</td>
<td></td>
<td>200pg/ml</td>
<td>50pg/ml</td>
<td>N/A</td>
<td>500-3000pg/ml</td>
</tr>
<tr>
<td>Aeron</td>
<td>&lt;100pg/ml</td>
<td>100-500pg/ml</td>
<td>100-500pg/mL</td>
<td>1000-10,000pg/ml</td>
<td></td>
</tr>
<tr>
<td>NSLHAP</td>
<td></td>
<td></td>
<td>60.82[2-12,150]pg/mL</td>
<td>median/limits</td>
<td></td>
</tr>
</tbody>
</table>
Urinary Testing
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.
Benefits of Urine Testing

• Patient can collect and send hormone test to lab-no staff needed
• Non stressful, atraumatic collection
• Only urine allows determination of all the estrogen metabolites
• Provides comprehensive array of metabolites
• Averages hormone level over 24 hours
• Best reflection of tissue metabolism???
Problems with urinary testing

- Inter-individual difference in estrogens and their metabolites are large (10-100 fold differences in premenopausal women)\(^1\)
- Urine ratio’s of 2/16 metabolites correlate, although are in much lower levels in breast than in urine. In one study 4OH estrogens were not measureable in breast tissue of women with cancer.
- Newer LC-MS/MS techniques suggest that earlier RIA or ELISA tests may not be accurate at low levels such as seen in menopause.\(^3\)
- Cannot be used with diuretics, renal disease
- Potential for incomplete or incorrect collection
Citations for previous slide: “Problems with urinary testing”


Things to remember about hormone testing:
Interrelationship of Hormones

- The ratio of various metabolites reflects the tissue relationship of these hormones and metabolic pathways (we think).
- Whereas levels of individual hormones and metabolites do not reflect local metabolism.
- These interrelationships are the same whether in a timed collection or random collection.

Wudy SA, Hartmann MF 2004. Horm Metab Res. 36:415-422
# Estrogens

<table>
<thead>
<tr>
<th></th>
<th>Blood</th>
<th>Saliva</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Can measure all 3, More data in the literature on what normal level is.</td>
<td>N/A</td>
<td>High levels of metabolites do not vary with route of delivery</td>
</tr>
<tr>
<td>Cream</td>
<td>Takes 6-8 weeks to equilibrate, levels may not change even with symptom improvement</td>
<td>E2, E3 actively transported into saliva. Levels higher than serum. Pre and post Rx not comparable</td>
<td>In addition E1/E2/E3 ratios, 2/16OH ratio, and 2 and 4 methoxy estrogens can be measured</td>
</tr>
<tr>
<td>Gel</td>
<td>Takes 4 weeks to equilibrate, levels reported to peak at 36hr</td>
<td>Can raise levels, pre and post Rx level not comparable</td>
<td>Much of the work on 2/16 ratios were done on urine</td>
</tr>
<tr>
<td>Vaginal</td>
<td>Levels are not increased, metabolites are</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Progesterone

<table>
<thead>
<tr>
<th>Route</th>
<th>Blood</th>
<th>Saliva</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Low luteal levels can be obtained but RR usually follicular level peaks at 6-8 hours</td>
<td>RR=follicular Not the recommended testing for oral or transbuccal routes</td>
<td>High levels of metabolites do not vary with route of delivery</td>
</tr>
<tr>
<td>Cream</td>
<td>Minimally increased levels. Depot in fat and take longer to equilibrate after dose change</td>
<td>Very high levels, may be due to contamination from hands/equipment, Tissue levels unknown</td>
<td>Must remember you are measuring downstream, conjugated metabolites:</td>
</tr>
<tr>
<td>Gel</td>
<td>Ability to raise serum levels. Tissue levels unknown. Levels peak at 3-4hr</td>
<td>Ability to raise salivary levels. Tissue levels unknown</td>
<td>(Pregnanediol-3-glucuronide is the primary metabolite)</td>
</tr>
<tr>
<td>Vaginal</td>
<td>Minimally increased levels</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Testosterone

<table>
<thead>
<tr>
<th></th>
<th>Blood</th>
<th>Saliva</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Reproducible, RR=follicular</td>
<td>Reproducible, RR=follicular, measures free</td>
<td>Metabolites measured:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Testosterone</td>
<td></td>
</tr>
<tr>
<td>Cream</td>
<td>Minimal change, takes 6-8 weeks to equilibrate</td>
<td>Levels higher than serum, RR created by labs adjusted upward</td>
<td>Test-sometimes measurable Etiocholanolone, androstenediol, and</td>
</tr>
<tr>
<td>Gel</td>
<td>Able to raise levels within hours, equilibrate with SHBG by 4 weeks</td>
<td>Levels elevated are achieved</td>
<td>Androsterone are all measurable</td>
</tr>
<tr>
<td>Vaginal</td>
<td>N/A</td>
<td>N/A</td>
<td>Levels do not vary with route of delivery</td>
</tr>
</tbody>
</table>
## DHEA

<table>
<thead>
<tr>
<th></th>
<th>Blood</th>
<th>Saliva</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>DHEA-S thought to reflect total body stores</td>
<td>Free DHEA measured</td>
<td>Levels are sensitive and reproducible</td>
</tr>
<tr>
<td>Cream</td>
<td>unknown</td>
<td>unknown</td>
<td>unknown</td>
</tr>
<tr>
<td>Gel</td>
<td>N/a</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Vaginal</td>
<td>Apparently do not increase</td>
<td>unknown</td>
<td>unknown</td>
</tr>
</tbody>
</table>
Deciding what to measure

• Ideally we would like to know levels of different hormone in target tissues such as brain and breast.
• Additionally we would like to know how that level is affecting the tissue so we can adjust the dosing of HRT.

DREAM ON!
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.
Why I don’t measure (female) hormones in saliva

• Some hormones (cortisol, DHEA, estrogens) map very closely to blood levels. Others (progesterone) do not. Effect of lipophilic nature of the hormone (issue of contamination of specimen by patient).

• I don’t believe there is enough data to say that salivary levels reflect what is going on in the tissues (although some believe they do)

• I want to be able to compare pre and post dosing levels
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-estrogens
- 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
SHBG: A functional test of hormone effect?

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

• I use it as a “functional” test of estrogen levels (total) in the body
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
Compounding
When you compound:

• Know your pharmacy (how often do patients complain, how often do your labs look strange, how responsive are they to your queries?)
• Make sure patients understand their responsibilities (to notice changes with new batches of hormones, to report symptoms, to get hormone levels, to take the hormones consistently)
• Make sure you know your risks and responsibilities (proper informed consent, proper follow-up, proper documentation)
Compounded hormones

ACOG Committee Opinion: “Most compounded products have not undergone rigorous clinical testing for safety or efficacy, and issues regarding purity, potency and quality are a concern.”
The thing everyone forgets in the compounding argument...

- We are allowed by the FDA to compound for patients who are allergic to the carriers (like peanut oil in Prometrium).
- We are allowed to compound to help patients be able to take their drugs more reliably and safely (making them in liquid form...or in this case putting all the hormones in one preparation so that patients don’t forget, overdose, or run out of one hormone)
Compounded hormones

Compounded hormone products have the same safety issues as those associated with hormone therapy agents that are approved by the U. S. Food and Drug Administration and may have additional risks intrinsic to compounding. There is no scientific evidence to support claims of increased efficacy or safety for individualized estrogen or progesterone regimens. That is not the same as saying they are not safe or preferable.
Reasons to Avoid Young Normal Levels After Menopause
My conclusion:

Regardless of what you call it (HT or HRT) or when you start it (pre-, peri, or post-menopause), as long as you consider menopause a “deficiency state” and replace women to “young normal levels” or use the oral route of administration of chemicals whose metabolic pathways and functions are only partially known...
You will struggle with

1. Paradoxes
2. unexpected outcomes
3. increased rates of diseases like breast cancer and cardiovascular disease
4. “chasing your tail” with more and more hormones trying to bring a complex evolving system that we only partially understand into healthy balance.
Treatment of the menopause with hormones
What do we know?
Reading the literature

• Most hormone regimens in the past aimed to replace estrogen to “young normal levels” (So most labs use this as their reference range for replacement).
• Progesterone and Progestins are mislabeled and intermixed.
• Menopause in earlier studies and some recent ones include women with and without ovaries.
• The earlier the study the more “menopausal women” are likely to be hysterectomized and/or oophorectomized and their symptoms related to surgery rather than menopause.
• Authors of studies are self-serving (publish or perish) and heavily manipulated by the pharmaceutical industry.
Making heads or tails of the studies:

• Some women are more at risk for breast cancer or heart disease or clotting than others – most studies do not break these out.

• Perimenopause and early and late menopause are very different hormonally and they get lumped together in studies. You have to break them out!

• Transdermal and oral hormones are vastly different in effects, side-effects, and safety.
What we know...and don’t know!

• No one has done a large randomized study of bioidentical, transdermal estradiol and continuous bioidentical progesterone.
• No one has looked at SHBG and testosterone issues and no one has done a RCT of bioidentical transdermal testosterone.
• There is no data on combining estriol with other estrogens let alone with testosterone and progesterone.
• We do not know much about hormone levels in tissues and nothing about the effect of various HRT formulations and routes of delivery on tissue levels.
Generally, as science-based practitioners we must view opinions from industry with care.
While “N of one” studies are arguably the most powerful form of evidence, we are wise to remember that “the plural of anecdote is not evidence.”
Estrogens - my conclusions

• Giving premenopausal doses of estrogen suggests that the practitioner believes that “Mother nature got it wrong.” Keep levels in the physiologic range for age.
• There is no point in giving an estrogen and an anti-estrogen that works competitively at the same time. Either give less of the estrogen or give the anti-estrogen alone (if there is too much endogenous estrogen and you want to block it)
• Estrogens should be given transdermally, preferably in gel form, to limit the amount given and to avoid first pass through the liver.
Progesterone Administration: route depends on desired effect

- Transvaginal - uterine first pass effect\(^1,2\)-may work better to treat endometrial proliferation.
- If transdermal, avoid fat depot premenopausally as it will be harder to get a brisk drop in progesterone. Serum levels can be sub-luteal and still protect the endometrium from proliferation without producing secretory changes in the endometrium (if given continuously).
- If given orally, expect larger brain effect and a need for higher doses due to first pass through the liver.
- Best blood levels are obtained with gels \(^3\) (follicular) but blood levels do not reflect tissue levels.
Citations for previous slide: “Progesterone Administration”


### Studies of Progesterone Cream

**STANCZYK ET AL**

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of subjects</th>
<th>Type of cream</th>
<th>Daily P dose (mg)</th>
<th>Duration of treatment (wks)</th>
<th>Mean P levels* (ng/mL)</th>
<th>Effect on endometrium</th>
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</thead>
<tbody>
<tr>
<td>Burry et al⁷</td>
<td>6</td>
<td>Pro-Gest</td>
<td>30 and 30 × 2⁵</td>
<td>2 for each dose</td>
<td>3.3</td>
<td>ND⁹</td>
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<tr>
<td>Carey et al⁵</td>
<td>24⁴</td>
<td>Progestelle</td>
<td>40 or 20 × 2</td>
<td>6</td>
<td>1.67</td>
<td>ND</td>
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<tr>
<td>Copper et al⁰</td>
<td>10</td>
<td>Pro-Gest</td>
<td>40-80</td>
<td>1.4</td>
<td>2.9</td>
<td>ND</td>
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<tr>
<td>Wren et al¹⁰,¹¹</td>
<td>27⁴</td>
<td>Pro-Feme</td>
<td>16, 32 or 64</td>
<td>2 in each of 3 cycles</td>
<td>&lt;3.5</td>
<td>Not secretory</td>
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<tr>
<td>Lewis et al¹²</td>
<td>24⁴</td>
<td>Compounded</td>
<td>0, 40 or 80</td>
<td>6</td>
<td>3.5</td>
<td>ND</td>
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<tr>
<td>Leonetti et al¹³</td>
<td>37⁴</td>
<td>Pro-Gest</td>
<td>0, 15 × 2, or 40 × 2</td>
<td>4</td>
<td>low¹⁰</td>
<td>Antiproliferative</td>
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<tr>
<td>Landes et al¹⁴</td>
<td>40</td>
<td>Pro-Gest</td>
<td>20</td>
<td>24</td>
<td>Not given</td>
<td>Atrophic in 2¹⁵</td>
</tr>
</tbody>
</table>

*Maximum levels achieved in serum or plasma.

⁵×2 indicates twice daily treatment.

⁶Not determined.

⁷Randomized to treatment groups.

⁸A progesterone-free week was included after the first 3 weeks.

⁹Actual values not stated.
Testosterone

• Can be used to evaluate ovarian function after menopause as it is the major excretory hormone from the ovary
• Can be used to modulate SHBG
• If methyltestosterone is dangerous for men, it may also be dangerous for some women even though the doses are much smaller
Address the matrix first!

Finding and replacing the RIGHT hormone.
What I do: Finding and replacing the right hormones

- Address the Matrix first
- Then, I measure hormone levels in blood and if possible in urine (at least the estrogen metabolites)
- If hormones are indicated I get an informed consent signed and document why I’m giving it and that the patient understands the risk and wishes to proceed
- I prescribe Joel Hargrove’s transdermal bioidentical formula (and tell the patient where I got the formula from)
Joel Hargrove’s transdermal compounded HRT

- Estradiol 150mg
- Progesterone 6 gms
- Testosterone 200mg

in 30 cc propylene glycol

Sig: apply one gtt to wrist and rub in with the opposite wrist. Do not touch the area for 30 minutes. Do not squeeze the bottle, allow the drops to fall out by gravity. Increase by 1 drop each week until you have titrated to “minimal hot flashes, not awakening with hot flashes at night, and NO BREAST TENDERNESS

Provides approximately .25mg/gtt estradiol, 10mg/gtt progesterone, and .33mg/gtt testosterone
What I do:

• When they have reached the right dose for them based on symptoms, they continue on that dose for one month
• Then I repeat blood levels
• If estradiol is still not measurable but metabolites have increased and they are symptom free I do not adjust estrogen levels
• If estrogen is too high, I adjust either the number of drops (downward) or the amount of estradiol in the formula
• I adjust the testosterone (and rarely, the progesterone) as needed
• After one month on the new formula, I retest
What I do long-term:

• I retest every one to two years until somewhere between age 60-65.

• At that point we discuss decreasing the dosage to bring estradiol levels in the range of 10-15pg/ml. At this point many women are o.k. to go off hormones altogether and we discuss whether they need them for bone or brain health.

• I use estriol vaginal cream for vaginal and urogenital symptoms with or without HRT drops.
Monitoring the endometrium

- All patients monitor for bleeding, spotting or brown discharge. If bleeding occurs I perform the usual workup
- I do not routinely do ultrasound or endometrial biopsies unless there are continued high levels of hormone or metabolite
Approach for demanding patients:

More and clearer informed consent. Have patient sign your note if:

1. they demand hormone therapy when levels are already adequate by lab testing
2. they have had breast or uterine cancer
3. they have had brain cancer
Approach for puzzling patients

• Get more information
• Titrate to symptoms then see where you are
• Remember most cancers don’t happen overnight but don’t leave people in incorrect set point states for long periods of time
Some patients require “convincing” that they need to work on their adrenals
How I give DHEA

• Compounded sublingual drops 1gtt=1mg
• Put one drop under the tongue for as long as possible then swallow.
• After one week increase the dose by one drop.
• Continue increasing slowly (by one drop per week) until you “feel better.” *Usually they will go beyond this point and have to decrease back to their ideal dose.
• After 6 months attempt to wean them off.
• Experiment with whether it is better to take AM or PM.
Why I give E/P/T drops

• Transdermal allows me to give fewer molecules that need to be metabolized.
• Combined drops allow convenience for the patient and less likelihood that they will forget, over or under dose, or run out of their HRT.
• Drops allow me to pulse (create rhythm) that I believe is more physiologic.
• Combined drops allow me to titrate to symptoms (estrogen related are easiest for patients to monitor) and adjust the ratio of the three hormones.
Why I use blood/urine metabolite testing

• Blood is the appropriate medium for gels
• I don’t have to wait longer than one month for dosage changes to equilibrate
• It is covered by insurance (except urine metabolites)
My conclusions:

• Many women need Functional Medicine NOT hormone replacement.

• Hormones balance each other, it can sometimes be difficult to identify the dysfunctional system.
Confounders:

• Bad compounding
• Bad instructions to patient
• Laboratory snafu’s
• Xenoestrogens???
Xenoestrogen Structure

Bisphenol A

PCB’s

Resveratrol

DDT

Equilenin
Conclusions:
Conclusions: Estrogens

- Estradiol is superior to other estrogens because it is more potent and therefore requires lower doses which have smaller effect on liver metabolism, and to CEE because of CEEs preferential metabolism down the 4OH pathway.
- Transdermal estradiol is superior to oral because there is no effect on clotting, hormone binding proteins, and smaller doses (1/10) are required.
- Estriol is an excellent therapy for the urogenital system when used vaginally in appropriate doses. There is inadequate evidence of it’s protective effect on the breast but it is unlikely to cause harm.
Conclusions: Progesterone

- Progesterone is superior to progestins because of a smaller effect as a SEEM, a superior cardiovascular profile and as a precursor and supporter of cortisol.
- Progesterone given orally can raise blood levels briefly, cause secretory changes in the endometrium if given in high enough doses, and is a GABA agonist.
- Progesterone given transdermally is problematic when given as a cream as it may depot in fat and may have a negative effect as a SEEM.
- Transdermal progesterone does not produce luteal phase levels or effects in the endometrium. (It appears to prevent endometrial proliferation especially if used transvaginally.)
- After menopause progesterone may have negative effects on the breasts.
Conclusions: Testosterone

• Testosterone is important to lower SHBG and “free” bound estrogen and testosterone. Little is known about bioidentical testosterone for women because there are no FDA approved versions.
Conclusions: Compounding

• Compounding pharmacies are a legitimate source of hormones that are not otherwise available (testosterone and estriol) if the practitioner is willing to shoulder the burdens of safety and lack of information.

• Compounding pharmacies are a legitimate way to combine hormone therapies for convenience of delivery, to avoid allergies, and to minimize patient under and overdosing.
Drinking from a fire hose...