“IT’S COMPLICATED: SEX, LIES, AND HORMONES”—THE TRAILER

2015 Mid America Pharmacy Conference
HORMONES...

Who needs them, anyway?
They say menopause makes women do strange things... LIKE SWALLOW HORSE URINE!

PREMARIN CONTAINS HORSE URINE

IF YOU TAKE PREMARIN, URINE FOR A SURPRISE!

What would you do if your doctor told you to swallow horse urine every day for the rest of your life? You’d recommend him or her to the funny farm, right? But what if your doctor handed you a bottle of pills called “Premarin”? If you were like 8 million other menopausal or post-hysterectomy women, you’d smile trustingly and take your medicine.

But Premarin, the most commonly prescribed drug in the U.S., has a nasty secret ingredient: pregnant mares’ urine.

To produce Premarin, pregnant mares are hooked up to rubber urine-collection bags and tethered in stalls so small they can’t even turn around or lie down comfortably. They are forced to stay there for six months, while their bodies are producing the most estrogen. Within days of giving birth in the spring, the mares are reimpregnated. Fertile mares may go through this same grueling cycle year after year.

The foals—all but a few kept for stud or to replace worn-out mares—will be sold at auction. From there, most go to feedlots to be fattened for slaughter. Mares, too, are slaughtered when they become lame or infertile. Look carefully at the label on a can of dog food and you may see them mentioned: meat byproducts.

The good news is that Premarin is the ONLY menopause drug made with animal-derived estrogen. Safe, effective alternatives include Genestin, Estratab, Estraderm, Estrace, Ortho-Est, and Rernifemin.

For more information and a list of alternatives, call 1-800-KNOW PMU.

People for the Ethical Treatment of Animals
501 Front St., Norfolk, VA 23510
757-622-PETA • www.MenopauseOnline.org
DEFINITION OF HORMONE:

- A chemical substance produced in the body that controls and regulates the activity of certain cells or organs

- Derived from the word “hormao” which means “to set in motion” or “to stir up”. It was used in ancient Greece to convey vital principle “of getting the juices flowing”
Steroid hormone biosynthesis begins in the mitochondria.

Receptors for estrogens, androgens and thyroid hormones are found in the mitochondria from many cell types.

Estrogen and testosterone play a protective role in the mitochondrial processes implicated in aging.

The mitochondria in brain cells also are affected by steroid hormones.

Thyroid hormones are critical to the function of the mitochondria.

Estrogens have a beneficial effect on mitochondrial function in the vascular system while muscle repair also is dependent on hormonal interaction with the mitochondria.

Post-menopausal obesity and insulin resistance may be due to skeletal muscle mitochondrial dysfunction caused by a drop in estrogen levels.
The mitochondria give birth to all hormones. Steroid hormone biosynthesis begins in the mitochondria because the conversion of cholesterol to pregnenolone — the precursor to all steroid hormones — occurs through the activity of the cytochrome P450 side-chain cleavage enzyme located on the inner mitochondrial membrane.

The electron transport chain of mitochondria is involved in testosterone production in the Leydig cells and manipulation of this pathway has been shown to increase production of testosterone.

Fig. 6. Possible mechanisms of mitochondrial dysfunction include (1) Mitochondrial DNA (mtDNA) mutation caused by free radical damage; (2) Krebs’ cycle decreased efficiency due to inadequate Krebs’ cycle intermediates; (3) Respiratory chain defect due to enzyme and substrate alterations; and (4) Membrane disorganization and loss of fluidity. (Rustin, P. et al. “Defective mitochondria, free radicals, cell death—Reality or myth-ochondria,” Mech Age Develop, 2000-206.)
Figure 7. Central Energy Pathway

Digestion and Assimilation
- FATTY ACIDS, GLYCEROL, CHOLESTEROL
  - Carnitine
  - Adipate
  - Suberate
  - Ethylmalonate

Intermediary Metabolism
- Oxaloacetate
  - Asp
  - Tyr
  - Phe
- Fumarate
  - Malate
  - B3
  - B2
- Succinate
  - Mg

Electron Transport and Oxidative Phosphorylation
- NADH
  - NADH Dehydrogenase
  - Coenzyme Q10
  - Hydroxymethylglutarate
  - Cytochromes
  - ATP
  - ADP + Pi
  - O2
  - H2O

Energy for muscle and nerve function and for building new tissue

Note: Vitamin & mineral requirements for cofactors are shown in light blue box. Elevations of metabolites before these steps indicate functional deficit of the nutrients.

Compounds Reported in ION™ Profile are Printed in Red
Receptors for estrogens, androgens and thyroid hormones are found in the mitochondria from many cell types.

Researchers have detected estrogen receptors in mitochondria of rat uterine and ovarian cells, MCF-7 breast cancer cells, cultured human lens epithelial cells and rat hippocampus and neuronal cells.

There are androgen receptors in mitochondria of human sperm cells. The androgen receptors were found in the midpiece region of sperm cells, home to a high concentration of mitochondria.
Estrogen and testosterone play a protective role in the mitochondrial processes implicated in aging.

β-estradiol and testosterone trigger a complex molecular mechanism that involves crosstalk between the mitochondria, nucleus and plasma membrane of the cell.

One of these other processes is mitochondrial-dependent testosterone production. With age, the mitochondria trigger the production of less and less testosterone.

This is why mitochondria are a common link between aging and infertility.

Estrogens and androgens protect the mitochondria against different insults. Many aspects of mitochondrial function and biogenesis are under estrogenic control, including mitochondrial state 3 respiration, the Krebs cycle and oxidative phosphorylation. The levels of mitochondria in many tissues are at least partially dependent upon androgens. This interplay between hormones and mitochondria impacts many areas of health.
REFERENCES FOR PREVIOUS SLIDE

  Wickramasekera NT and Das GM. Mitochondrion. 2014 May;16C:26-37.


Cold and high-calorie diet stimulate the sympathetic nervous system leading to the release of norepinephrine. NE triggers the activation of the β-adrenergic receptors (AR) resulting in the elevation of intracellular cAMP and inducing the expression of PGC-1. PGC-1 activates the expression of the subunits of respiratory chain and mtTFA through the induction of the expression of NRFs and the coactivation of NRF-1-mediated transcription. mtTFA subsequently translocates into mitochondrion and directly activates the transcription and replication of mtDNA. Cell
ENENVIRONMENT (Cold, Diet)

↑Sympathetic Nerve Activity

NE

AR AR AR

↑cAMP

↑PGC-1

Nuclearly encoded subunits of mitochondrial respiratory chain (e.g. COX IV, ATP synthetase), mtTFA

mtTFA

Mitochondrial Replication and Transcription

Mitochondrion

Nucleus
WHERE HAVE ALL THE HORMONES GONE?-"GONE WITH THE WIND"

- Dec. by OC’s
- Dec by tubal ligation
- Dec by hysterectomy
- Dec by oophorectomy
- Dec by vasectomy
- Dec by multiple pregnancies
- Dec by harmful EMF exposure
- Menopause & andropause
- Dec by miscarriages & terminated pregnancies
- Dec by stress adaptation
- Dec by medications
- Dec by physical anomalies
- Dec by lack of exercise
- Dec by nutritional deficiencies
- Dec by xenobiotics
XENOESTROGENS
“GRAPES OF WRATH”

- Substances foreign to human body that resemble and act like estrogens
- Derived from petroleum products, therefore, they are fat soluble
- Plastics-Nonylphenols, Bisphenols, phthalates
- Organic Chlorinated Pesticides
  - DDT, endosulfan, atrazine, 2,4-D, dioxins, PCB’s, styrene, phthalates, nonylphenols
- Highest accumulation in Dairy Products, Chicken, Turkey, Beef, Pork, Water, Corn, Sugar, Contaminated Fish (descending order)
**XENOESTROGENS & XENOBIOTICS**

- U.S. has the highest incidence of Breast Cancer in the World
- Rise since 1950 from 1 in 20, to 1 in 7 women
- World Health Organization (1964): 80% of all cancers due to synthetic carcinogens
- Many industrial workers are at 10x the risk of developing cancer
  - their children are at a higher risk—i.e. childhood leukemia 2-5x greater incidence if father worked with spray paints and dyes
- WHAN (Women’s Health Action Network) of Seattle
- WEDO (Women’s Environmental & Development Organization)
- NCAMP (National Coalition Against the Misuse of Pesticides)
CONCERNS IN TODAY’S WORLD OF HRT

- Media reported over & over on 3 studies done on foreign substances, Premarin & Provera

- This is not new information

- Used term “estrogen”---a class of related analogues not a single substance

- Unnecessary step back in time

- Negative press does not negate cellular & biological studies from the early 1900’s on the roles of endocrine molecules in human physiology or cantaloupe physiology!
FUNCTIONS OF BIO-IDENTICAL PROGESTERONE
“IT’S DELOVELY”

- Antioxidant
- Increases libido
- Prepares breast for lactation
- Diuretic - Tells the kidney to rid body of excess sodium and water
- Prepares uterus for implantation
- Prevents & reverses fibrocystic breast disease
- Saves pregnancies
- Helps regulate blood sugar levels
- Natural Anti-depressant
- Anti-convulsitive
- Decreases number of estrogen receptor sites
- Thermogenic
- Non Carcinogenic, induces apoptosis of cells
- Thickens vag secretions
- Inhibits human cancer cell growth & invasiveness
FUNCTIONS OF PROGESTERONE, (CON’T)  
“MY FAIR LADY”

- Normalizes zinc & copper levels
- Escorts T3 across mitochondrial membrane
- Increases SHBG levels
- Skeletal Muscle Relaxant
- REM Sleep
- Vasodilation via inc. Nitrous Oxide release
- Adds to estrogen protection of glutamate toxicity
- Normalizes blood clotting
- Lowers blood pressure
- Decreases Vascular Proliferative and Inflammatory Responses
- Decreases Sympathetic Activity
- Immunosuppressant
FUNCTIONS OF PROGESTERONE, (CON’T)

- Helps the lining of the uterus mature in the second half of the cycle
- Modulates estrogen distribution across the tissues
- GABA receptor agonist (neuroinhibitory)
- Stimulates osteoblastic and inhibits osteoclastic function (bone trophic)


– protects arterial linings

– Protects hippocampus

<table>
<thead>
<tr>
<th>Sex Characteristics</th>
<th>Improves lipid profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proliferates endometrium</td>
<td>Dec triglycerides</td>
</tr>
<tr>
<td>Thins cervical mucus</td>
<td>Stimulates reverse cholesterol transport</td>
</tr>
<tr>
<td>Prevents &amp; treats cervical dysplasia</td>
<td>Lowers blood pressure</td>
</tr>
<tr>
<td>Libido and Orgasm</td>
<td>Normalizes blood clotting</td>
</tr>
<tr>
<td>Primes testosterone receptor site</td>
<td>Strengthens heart valves and venous valves</td>
</tr>
<tr>
<td>Dec. risk of CVD</td>
<td>Inc. stroke volume</td>
</tr>
<tr>
<td>Promotes normal Heart rhythms</td>
<td>Inc flow acceleration</td>
</tr>
<tr>
<td>Dec plasma renin substrate</td>
<td></td>
</tr>
</tbody>
</table>

**MORE FUNCTIONS OF E₁, E₂, E₃**

**“HERE’S LOOKIN AT YOU, KID”**

- Promotes neural cell growth
- Improves cerebral glucose utilization
- Improves synaptic activity
- Improves cerebral blood flow
- Protects brain from glutamate toxicity
- Improves cognitive function

- Reduces risk of senility/Alzheimer’s
- Natural antidepressant
- Maintains REM sleep
- Decrease in symptoms of Parkinson’s Disease
- Promotes emotional stability
- Increases desire to compete in life
- Prevents morbidity
- Protects the pancreas

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EVEN MORE FUNCTIONS OF E₁, E₂, E₃

Antioxidant

Increases energy production

Blocks receptor sites from Xenoestrogens Dec. risk of colon cancer

Slows calcium loss from bones

Prevents macular degeneration, dry eye syndrome, cataracts, & most ocular diseases

Improves fat to muscle ratio


“WORKING GIRL”
MORE FUNCTIONS OF E₁, E₂, E₃

- Helps to maintain body temperature
- Delay Memory Loss
- Regulates brain segments that prepare the body for sexual and reproductive development
- Regulates production of cholesterol in the liver, decreasing build up of plaque in coronary other arteries
- Stimulates maturation and maintenance of thick vaginal lining as well as lubrication
Brain mitochondria from rats given the hormones had enhanced functional efficiency and increased metabolic rates. The hormone-treated mitochondria also were marked by increased respiratory function and increased expression and activity of the electron transport chain complex IV. This increased respiratory activity occurred together with a decreased rate of reactive oxygen leak and reduced lipid peroxidation indicating there was a systematic enhancement of brain mitochondrial efficiency.

"Ovarian hormone replacement induces mitochondrial alterations in the central nervous system supporting efficient and balanced bioenergetics reducing oxidative stress and attenuating endogenous oxidative damage."

Additionally, estrogen ameliorates the memory decline that occurs after menopause. Working memory — which declines with age — is dependent upon the excitation of neurons within the dorsolateral prefrontal cortex (dlPFC).

The scientists investigated the effects of estrogen administration to test whether this treatment—known to improve working memory—influences mitochondrial shape.

Diagram: JJ T. Eells, et al. from the Department of Pharmacology and Toxicology, Medical College of Wisconsin
Aged ovariectomized monkeys treated with a control experienced significantly impaired working memory and an increase in presynaptic donut-shaped mitochondria. Estradiol treatment reversed both the impaired working memory and the increase in donut-shaped mitochondria.

The researchers concluded, "Our data suggest that hormone replacement therapy may benefit cognitive aging, in part by promoting mitochondrial and synaptic health in the dlPFC (dorsolateral prefrontal cortex)."

Estrogen stimulates Acetylcholine for attention & memory, etc, Serotonin for mood & melatonin, Dopamine for fine motor skills, mood Norepinephrine for attention and cognition

ALZHEIMER’S DISEASE

- Folding of amyloid beta protein is the pathogenic event in Alzheimer’s.

- Estrogens inhibit the oligomer formation, with estriol being the strongest inhibitor.

- Physiologic levels of hormones delay progression of disease.

NEUROPROTECTIVE

- Estradiol, progesterone, and androgens
  - Estrogen
    - Activation of signaling molecules and interactions with growth factors
    - Effects dopamine signaling pathway
  - Women with low estrogen often have low dopamine and serotonin levels when urine is tested
Biomarkers for cellular aging – Telomere length
  – Telomerase activity
  – HRT for 1 year or longer

– Longer endogenous exposure associated with greater telomere length and lower telomerase activity

“A FEW DEGREES OF SEPARATION”

Natural (bio-identical) vs. Synthetic
PROGESTERONE (THE ONE AND ONLY)

Receptors and thus, the body, are exquisitely sensitive to seemingly minor changes in this molecule.
MEDROXYPROGESTERONE
“SHOW ME THE MONEY” - JERRY MCGUIRE
Figure 63-3. Principal pathways for biosynthesis of adrenocorticosteroids and adrenal androgens.
Figure 61-1. The biosynthetic pathway for the estrogens. Additional details and structures are shown in Figure 63-3 (page 1472).
Medroxyprogesterone Acetate USP
Pregn-4-ene-3,20-dione, 17-(acetoxy)-6-methyl-. (6a):
Provera, Depo-Provera (Upjohn)

Estradiol NF
Estra-1,3,5(10)-triene-3,17-diol, (17β)-: 17-Beta-estradiol; Dihydrotheoid:
(Merrell-National); Progynon (Schering)

Fludrocortisone Acetate USP
Pregn-4-ene-3,20-dione, 21-(acetoxy)-9-fluoro-11,17-dihydroxy-. (11α):
Florinef Acetate (Squibb)
SIDE EFFECTS OF PROGESTINS

- Increases sodium and water retention
- Causes depression
- Cannot maintain pregnancy
- Increases appetite and weight gain
- Carcinogenic
- Blood clots lungs, periphery, brain
- Hair loss

- Masculinizes the female fetus
- Can be estrogenic or androgenic
- Cannot be synthesized into other compounds
- Cannot raise basal temperature
- Acne & facial hair growth
- Impaired glucose tolerance
MORE SIDE EFFECTS OF PROGESTINS

- Breakthrough bleeding
- Fibrocystic breasts
- Headaches & migraines
- Cardiac arrest
- Nausea
- Cholestatic jaundice
- Diarrhea
- Irritability/moodiness
- Seizures

- Lethargy
- Anxiety/panic/anger
- Insomnia
- Dysrhythmias
- Poor lipid profile
- Elevated BP
- Skeletal muscle spasms overall tightness
- Dec immune function & stress adaptation
ADDITIONAL OBSERVATIONS IN OC USERS

- Altered Immune Factors
- Altered Inflammatory Factors
- Vitamin Deficiency
- Magnesium, Folic Acid, B2, B6, B12, Vitamin C and Zinc


ADDITIONAL OBSERVATIONS IN OC USERS

- Increased Insulin resistance and Glucose Intolerance
- Elevated Cholesterol and Triglycerides
- Increased C-Reactive Protein
- 3-6 fold increase risk of venus thrombosis
- 2-5 fold increase of Mi’s and Stroke
- Increased Hepatocytes CRP synthesis
REFERENCES FOR PREVIOUS SLIDE


- Fisch IR, Freedman SH. Smoking, oral contraceptives and obesity. Effects on white blood cell count. JAMA 1975;234(5):500-6
The presence of serum immune complexes such as antiethinylestradiol and anti progestogen antibodies cause vascular lesions and other inflammatory cytotoxic conditions including thrombosis. These form in as little as 3 weeks.

Researchers confirmed that the immune complexes are not formed against non synthetic hormones.
- World Health Organization. Improving access to quality care in family planning. Published 1996. Revised 2001


ORAL CONTRACEPTIVES

- Increased risk of lupus, Rheumatoid Arthritis, Crohn’s and Ulcerative Colitis
- increased incidence of severe periodontitis, periodontal pockets and gingival inflammation
- Increased inflammatory immune cytokines
REFERENCES FOR PREVIOUS SLIDE


ORAL CONTRACEPTIVES

- Elevated WBC’s in OC users
- Increased hospitalization for inflammatory diseases of the respiratory, digestive, urogenital and musc skeletal of women under age 40 that use OC’s

FUNCTIONS OF TESTOSTERONE
“THE DARK NIGHT RISES”

- Produced in adrenals and testicles in men
- Produced in adrenals, skin, adipose tissue, muscles, brain, and ovaries in women
- Male secondary sex characteristics
- Anabolic: increases MM and bone mass and all collagen
- Increases libido in both men and women
- Improves memory
- Reduces body fat
- Positive lipid profile, stroke prevention
- Desire to compete in game of life
- Necessary for energy and sense of well-being
FUNCTIONS OF TESTOSTERONE
“I COULD O’ BEEN A CONTENDER”

- Antioxidant
- Necessary for collagen formation
- Improves neural cell formation
- Decreases SHBG
- Required for optimal transport of excess cholesterol from tissues and blood vessels back to the liver
- Enhances HDL-induced reverse cholesterol transport from arterial walls

- Decreases platelet aggregation
- Improves all tissue stamina
- Improves cognitive function
- Levels are decreased by 250 drugs
- Elevates hepatic lypase necessary for the liver to safely clear the body of excess cholesterol
MORE FUNCTIONS OF TESTOSTERONE

- Necessary for emotions of confidence, joy, affection, friendliness
- Is lowered by OC’s
- Is protective of autoimmune diseases
- Is inc’d by weight training & exercise
- Is dec’d by menopause & oophorectomies

- Is lowered by over 250 drugs
- Prevents platelet aggregation
- Lowers blood pressure
- Is lower in Andropause and BPH
- Lowered by environmental toxicities
TESTOSTERONE BENEFITS
“OF MICE AND MEN”

- Physiologic levels protect against prostatic hyperplasia
- Preserves sexual function
<table>
<thead>
<tr>
<th>Hormone Status</th>
<th>Three-Year Survival Rate</th>
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</thead>
<tbody>
<tr>
<td>High levels of DHEA, testosterone, and IGF-1</td>
<td>83%</td>
</tr>
<tr>
<td>Deficiency in one hormone (DHEA, testosterone, or IGF-1)</td>
<td>74%</td>
</tr>
<tr>
<td>Deficiency in two hormones (DHEA, testosterone, or IGF-1)</td>
<td>55%</td>
</tr>
<tr>
<td>Deficiency in all three hormones (DHEA, testosterone, or IGF-1)</td>
<td>27%</td>
</tr>
</tbody>
</table>

TESTOSTERONE BLOOD LEVELS AND SUBSEQUENT INCIDENCES OF DISEASE AND DEATH

<table>
<thead>
<tr>
<th></th>
<th>Highest Testosterone</th>
<th>Next to Highest Testosterone</th>
<th>Next to Lowest Testosterone</th>
<th>Lowest Testosterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-Cause Mortality</td>
<td>41% Reduction</td>
<td>38% Reduction</td>
<td>25% Reduction</td>
<td>Highest rate of Death</td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td>48% Reduction</td>
<td>41% Reduction</td>
<td>29% Reduction</td>
<td>Highest rate of Death</td>
</tr>
<tr>
<td>Cancer</td>
<td>29% Reduction</td>
<td>23% Reduction</td>
<td>26% Reduction</td>
<td>Highest rate of Death</td>
</tr>
</tbody>
</table>

ESTROGEN DISTRIBUTION (ENDOGENOUS)

- Secreted directly to the blood stream
- Travels directly to tissues via the inferior vena cava
- Returned to the liver after exerting its affect on tissue receptor sites for methylation and conjugation
ESTROGEN DISTRIBUTION (TRANSDERMAL/TRANSMUOCOSAL)

- Transmucosal- Same as exogenous

- Transdermal- Same as exogenous except when applied to abdominal skin
  - Transformation in subcutaneous adipose to other molecules
  - Subcutaneous adipose deposition for later release
  - TD/TmM does not have the same impact on liver, clotting factors

Ref 17-19
ESTROGEN DISTRIBUTION (ORAL)

- Significant processing through gut lumen and in gut endothelial cells
- Travels to the portal circulation
- Liver transformation and metabolism
- Only 10% of dose is bio-available
- 90% is converted into bioactive, untoward metabolites before absorption

Ref - #6 and 7
METABOLISM OF ESTROGENS

- After oral and intravenous administration of E2 - 50% is converted to E1
- CYP450 phase 1 oxidation - 16-alpha hydroxylation (estrogen dependant diseases- lupus and breast cancer), 2 - alpha hydroxylation, (protective) 4 hydroxylation- (DNA damaging quinone)
- Phase 2 conjugation - sulfation, methylation, glucuronidation of 2-, 4-, 16-hydroxylated compounds
- Phase 3 excretion in bile or urine
SIDE EFFECTS OF ORALLY ADMINISTERED ESTROGEN

- Migraine headaches
- Increases Estrone, not Estradiol levels
- Increases triglycerides
- Increases blood pressure
- Carcinogenic
- Cholelithiasis
- Sat of Cytochrome P450
- Gallbladder Disease
- Bloating
- Depression
- Thromboembolism
- Increase in Fibrocystic Breast Disease
- Competes with hepatic conversion of HGH to IGF-1 (Dec 1GF-1)
CHANGES IN HEPATIC PROTEIN SYNTHESIS WITH ORAL ESTROGENS

“THE FUGITIVE”

- Prothrombotic
- Inc fibrinogen I&II
- Dec TFPI (Tissue Factor Pathway Inhibitor)
- Inc CRP( X2)
- Inc Factor VII
- Dec D-Dimer
- Dec Plasminogen Activator Inhibitor Type I
- Dec circulating Antithrombin III
- Inc Renin
- Inc IGF-1 clearance & induction of GH resistance
- Promotes insulin resistance
- 16-alpha hydroxyestrone & other psycho hormones
- Inc triglycerides
- Dec lipid oxidation, inc fat mass
DOSAGE FORMS

- Orally Ingested
  - In Oil Suspension
  - Sustained-Release
- Rectal/Vaginal
  - Suppositories
  - Pessaries
  - Emulsions
- Implants
DOSAGE FORMS (CONT’D)

- Injectable
- Topical
  - Enhanced Absorption Bases
  - Hydrophilic Creams
  - Ointments
- Buccal
  - Troches
  - Sprays
  - Drops
EVALUATION OF PATIENTS

- Laboratory Studies
  - Saliva testing
  - Blood testing
  - Timing of the testing
  - Testing with creams vs. troches
HORMONAL MONITORING

- Serum - bound fractions:
  - Total estrogens, E2, DHEA, DHEA-S, Testosterone, etc.
  - Expensive, but insurance usually covers
  - Most accurate

- Saliva - unbound (free-floating) fractions:
  - Full panel of sex hormones, adrenal steroids
  - Least expensive
  - Least accurate

- Urine - conjugated forms:
  - E1, E2, E3, and other steroids; useful for metabolic errors
  - Most expensive
## Hormone Dosing and Monitoring (Progesterone)

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>Saliva Concentration</th>
<th>Serum Concentration</th>
<th>Capillary Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Luteal Phase</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luteal Phase Saliva</td>
<td>0.1-0.3ng/ml</td>
<td>12-32ng/ml</td>
<td>12-32ng/ml</td>
</tr>
<tr>
<td>Luteal Phase Serum</td>
<td>12-32ng/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luteal Phase Capillary</td>
<td>12-32ng/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buccal Troche 100mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Troche Saliva 1000-3000ng/ml</td>
<td></td>
<td>27-30ng/ml</td>
<td>270-300ng/ml</td>
</tr>
<tr>
<td>Transdermal Progesterone 20-30mg</td>
<td></td>
<td>10-30ng/ml</td>
<td>20-30ng/ml</td>
</tr>
<tr>
<td>Capsules 100mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capsule Saliva 0.2-0.4ng/ml</td>
<td></td>
<td>2-4ng/ml</td>
<td></td>
</tr>
<tr>
<td>Capsule Serum 2-4ng/ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capsule Capillary 2-4ng/ml</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
IS THERE SAFE & EFFECTIVE ENDOCRINE SUPPLEMENTATION?

I believe there is if we learn from our mistakes and follow a few integral principles...
PRINCIPLES OF NATURAL HORMONE REPLACEMENT

- Use only bio-identical hormones (natural human hormones)
- Use the safest route of administration (buccal)
- Preserve the delicate balance
- Individualize the dose
- Eat a Diet void of Xenobiotics & rich in fruits and vegetables
- Supplement with MVM, antioxidants, EFA’s
FAQS

- Tri-est vs Biest? 80% E3 10% E2 10% E1 VS 80% E3 20% E2
- Do we recommend progesterone if there is no uterus?
- Creams vs suppositories vs capsules vs troche vs pellets
Miller A, Raison C. Immune system contributions to the pathophysiology of depression. Jour Am Psych Assoc. 2008;6:36-45
Dantzer R, Kelley KW, Twenty years of research on cytokine-induced sickness behavior, Brain Behav Immun. 2007;21(2):153-60
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- Screaming to be Heard, Elizabeth Vliet, M.D.
- The Hormone of Desire, Susan Rako, M.D.
- What your Dr. may not tell you about Menopause, John R. Lee, M.D.
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