Estrogen

DEVIL or ANGEL?

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Disclosures

- **The following potential conflict of interest relationships are germane to my presentation:**

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- **Employment: Clearfield Medical Group**
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- **Status of off-label use of devices, drugs or other materials that constitute the subject of this presentation: NA/Non-Clinical**

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Objectives

1. Review Estrogen Synthesis and Function
2. The Elephant in the Room: Does Estrogen Cause Cancer?
3. Review the controversy “Natural vs. Synthetic Estrogen.”
4. Review Estrogen Metabolism
5. Discuss Estrogen and Brain Function
6. Review Estrogen Deficiency Symptoms
7. Review Estrogen Dominance Symptoms
8. Review the Laboratory Studies Related to Estrogen
9. Review Treatment Strategies to Safely Restore Estrogen to Youthful Physiologic Levels
10. Discuss Physiologic and Supraphysiologic Estrogen Levels in Men
11. Case Histories

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Marie R:

CC: 65 y/o female w hx of poorly controlled thyroid s/s, hot flashes, night sweats, vaginal dryness, depression, poor libido, fatigue. "Feels slow."

PH· Depressive disorder
HTN
Hypersomnia with sleep apnea, *mild, not on CPAP*
Hypothyroidism
Morbid obesity, BMI not known (HCC), *sip gastric bypass*
Primary localized osteoarthrosis, lower leg
Urinary incontinence

FH: Alcoholism, Dementia

Meds:

Aspirin 81 mg, Ginkgo
Escitalopram Oxalate (Lexapro) 20 MG Oral Tablet
Levothyroxine Sodium 137 MCG Oral Tablet
Prilosec 20 mg
Tolterodine Tartrate (Detrol LA) 4MG Oral Capsule Extended Release 24 Hour

Marie R:

BP 108/68 Pulse 80 I Temp (Src) 98.7 (Tympanic) I Resp 181 Ht 5' 3.7'' (1.618m) I Wt. 215 lbs 14.4 oz (97.932kg) IN BMI 37.41 kg/m2 I BSA 2.1 m2 I Sa0 2 97[room air[%

PE: General: Normotensive, in no acute distress.

Eyes: PERRLA, EOMI full, conjunctiva clear, eyebrows nearly absent

Neuro: Hyporeflexic biceps, patellar

Vaginal atrophy, some evidence of lichen sclerosus

2/26/17	*Marie*	*Median*		*Marie*	*Median*
Testosterone Free	1.3 pg/ml	2-4 pg/ml*	TSH	4.30	<2.5
Testosterone Total	19.0 ng/ml	<44 ng/ml*	free T3	1.9	>2.5
DHEA-S	77 ug/dl	195 ug/dl*	free T4	1.42	>1.5
Estrone (E1)	42 pg/ml	< 200 pg/ml*	rT3	328	80-250
Estradiol (E2)	<0.5 pg/ml	90 pg/ml*	T3/rT3	0.58	>1.06
Progesterone	0.10 ng/ml	5-7 ng/ml	TPO	462	<35
Pregnenolone	108 ng/dl	100 ng/dl*	TAG	179	113
EP Ratio	420	< 250			
P/E Ratio	inf	100-500			

Other: 25 OH D 41 Homocysteine 14.2 Hct 37.5, cRP 2.07, Insulin 15, FBS 101

Julia R.

37 y/o female presents w hx of TBI

Presents for Weight Control

% fatigue, "short fuse," Inattention, Poor memory

PH

(S06.9X0S) Unspecified intracranial injury without LOC

(N60.19) Diffuse cystic mastopathy of unspecified breast

(R53.83) Other fatigue

(F32.9) Major depressive disorder, single episode, unspecified

(K31.84) Gastroparesis

Heavy, Painful Menses, Irregular

S/P Cholecystectomy

ROS: *Fatigue, fibrocystic breasts, Hx. of Gallbladder disease,* Headaches, Mood Swings, Osteopenia, 16 cm fibroid, urinary urgency, frequency

PE: 67"; 258#; BMI 40.41; Bp 122/76; P77; O_2 Sat. 95%

Abd: 4 healed incisions from Lap. chole.

Uterus 18 week size fibroid

Julia R.

Meds:ARIPiprazole 5 MG Oral Tablet 1/d

Fluoxetine HCl 20 MG Oral Capsule 1/d

Oxycodone w/ APAP 10-325 MG 1 po q 4 hrs. prn

Metoclopramide 10 mg 1 po tid w meals

Labs Ordered:

CBC, BMP, Testosterone, free, total, IGF-1, Estrone, Estradiol, Progesterone, TSH, free T3, free T4, TPO, rT3, insulin, DHEA-S, Vitamin D, cRP, homocysteine, HbA1c, Lipid Panel., Pregnenolone, Cortisol, AM, ACTH, Prolactin, UA, urine c&S

Radiology: US Pelvis

Julia R.

	Julia	Median
Testosterone Free	1.3 pg/ml	2-4 pg/ml*
Testosterone Total	19.0 ng/ml	<44 ng/ml*
DHEA-S	77 ug/dl	195 ug/dl*
Estrone (E1)	274 pg/ml	< 200 pg/ml*
Estradiol (E2)	191 pg/ml	90 pg/ml*
Progesterone	0.06 ng/ml	5-7 ng/ml*
Pregnenolone	66 ng/dl	100 ng/dl*
EP Ratio	7750	< 250

	Julia	Median
TSH	1.13	<2.5
free T3	3.5	>2.5
free T4	1.28	>1.5
rT3	138	80-250
T3/rT3	2.53	>1.06
TPO	0.7	<35
TAG	0.2	<1

cRP	5.71	(normal 0-3, goal <1.0))
25 OH D3	17	(normal 30-100, goal 50-80
Homocysteine	10.8	(normal <11, goal <10)
IGF-1	128	(Goal 200-250)

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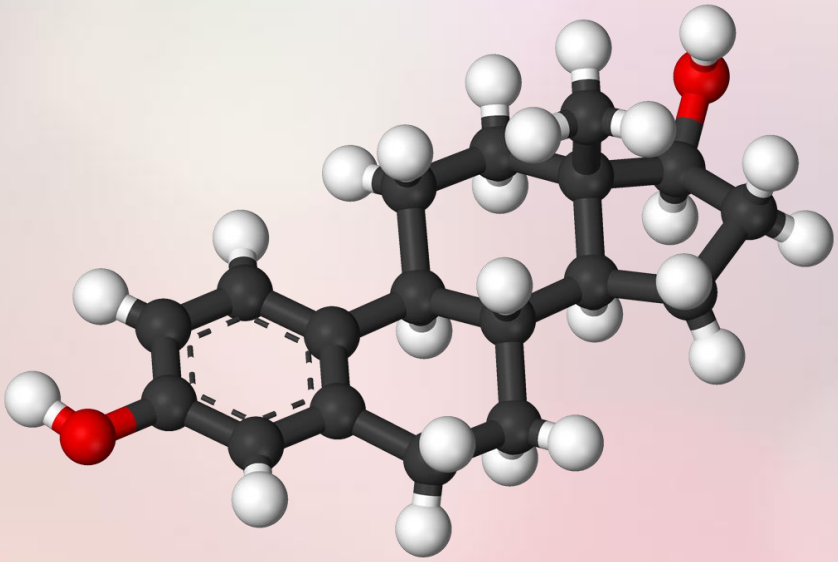
Estrogen

- **Major Female Sex Hormone**
  - **Produced In:**
    - **Ovaries *** (*Majority*)**
    - **Placenta (when Pregnant)**
    - **Adrenal Glands**
    - **Breast**
    - **Fat Cells**



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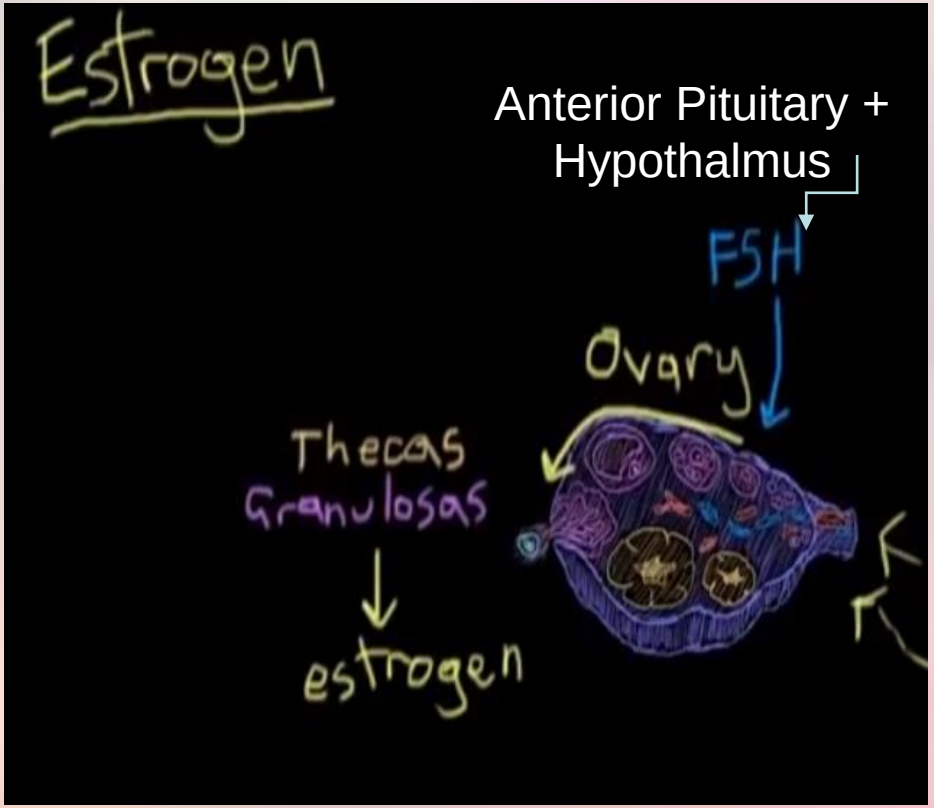
Estrogen Synthesis

- **Anterior Pituitary**
  - **FSH**
    - **Ovaries**
      - **Theca Cell**
      - **Granulosa Cell**

        » **ESTROGEN**



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Estrogen Has 400 Functions

- Stimulates the production of choline acetyltransferase, an enzyme which prevents Alzheimer's disease
- *Increases metabolic rate*
- *Improves insulin sensitivity*
- Regulates body temperature
- Helps prevent muscle damage
- Helps maintain muscle
- Improves sleep
- Reduces risk of cataracts
- Helps maintain the elasticity of arteries
- *Dilates small arteries*
- *Increases blood flow*
- Inhibits platelet stickiness
- *Decreases the accumulation of plaque on arteries*
- Enhances magnesium uptake and utilization
- *Maintains the amount of collagen in the* skin

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Estrogen Has 400 Functions

- *Decreases blood pressure*
- *Decreases LDL and prevents its oxidation*
- *Helps maintain memory*
- *Increases reasoning and new ideas*
- Helps with fine motor skills
- Increases the water content of skin and is responsible for its thickness and softness
- Enhances the production of nerve-growth factor
- Increases HDL by 10 to 15%
- *Reduces the overall risk of heart disease by 40 to 50%*
- Decreases lipoprotein(a)
- *Acts as a natural calcium channel blocker*
- *Enhances energy*
- *Improves mood*
- *Increases concentration*
- *Maintains bone density*
- Helps prevent glaucoma

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Estrogen Has 400 Functions

- Increases sexual interest
- Reduces homocysteine
- Decreases wrinkles
- Protects against macular degeneration
- Decreases risk of colon cancer
- Helps prevent tooth loss
- *Aids in the formation of neurotransmitters in the brain such as serotonin which decreases depression, irritability, anxiety, and pain sensitivity*
- Preserves bone structure-delays osteoporosis

Smith, P; *What You Need to Know About Female Hormones,* Lecture Notes, October 8, 2017, OMED, Philadelphia, PA.

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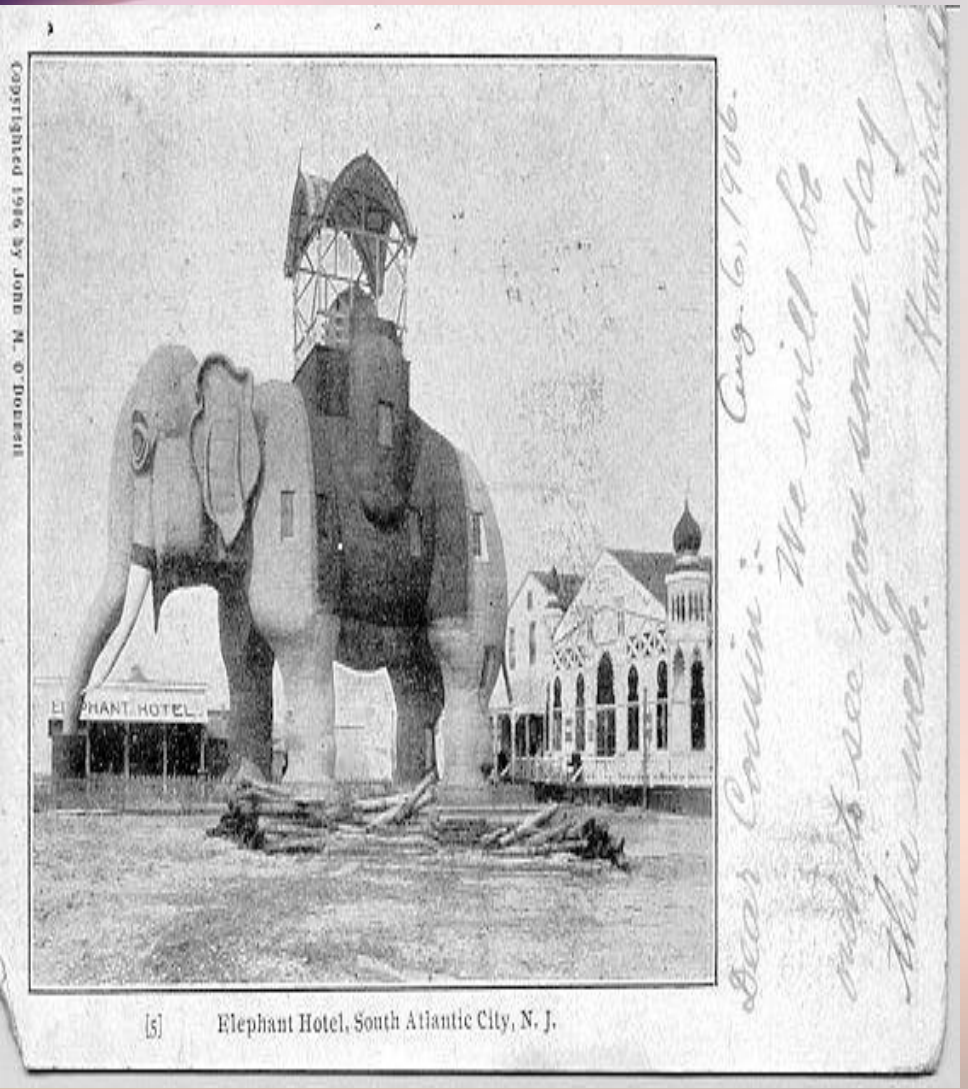
The Elephant In the Room: Estrogen Causes Cancer



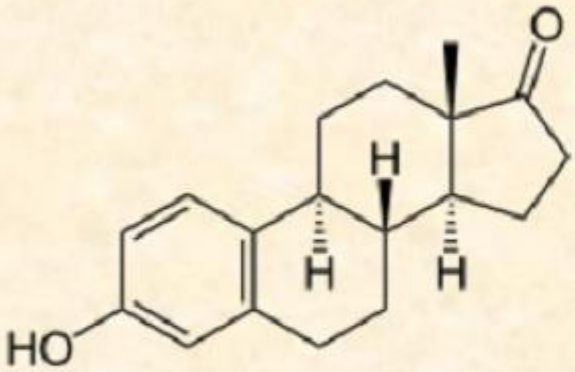


2002 WHI Study—"HRT" is Dangerous!

- Premarin® alone given to older postmenopausal women caused adverse effects in the **first year** (strokes, blood clots)
  - Oral estrogens cause blood clots, transdermal estradiol does not
- Adding Provera® (Prempro®) caused more adverse effects (breast cancers, heart attacks, dementia)
  - Provera increases breast cancer and vascular inflammation. Progesterone does neither.
- Thousands of lawsuits pending; drug companies running a legal-protection propaganda campaign to paint all "hormones" as equally dangerous!

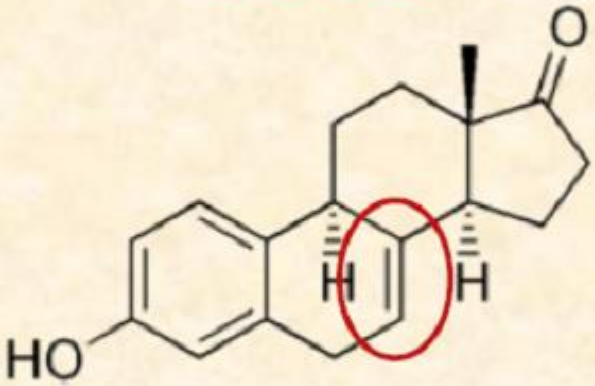
Premarin®
Conjugated Equine Estrogens

Human



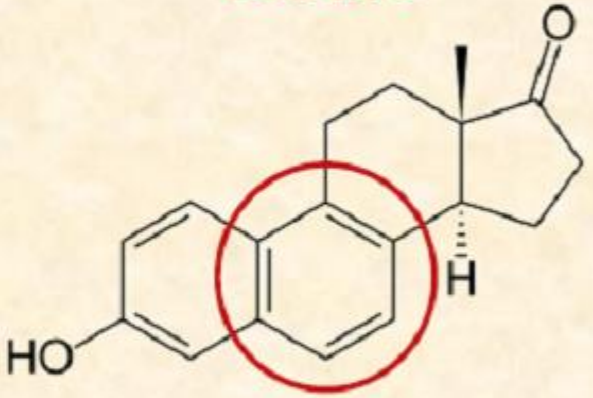
Estrone

Horse



Equilin

Horse



Equilenin

CEE contains at least 10 estrogens, only 3 are human; also contains horse androgens and progestins.

Klein R The Composition of Premarin. 1998 Int J Fertil 43:223

Natural Vs. Synthetic Estrogen

Natural Estrogen

- Defined as the same chemical structure that the patient is born with.
- It may or may not come from a plant.
- Natural estrogen helps to protect against endothelial dysfunction by increasing endothelial nitric oxide.
- Protects against heart disease, dementia, osteoporosis
- Improves insulin sensitivity

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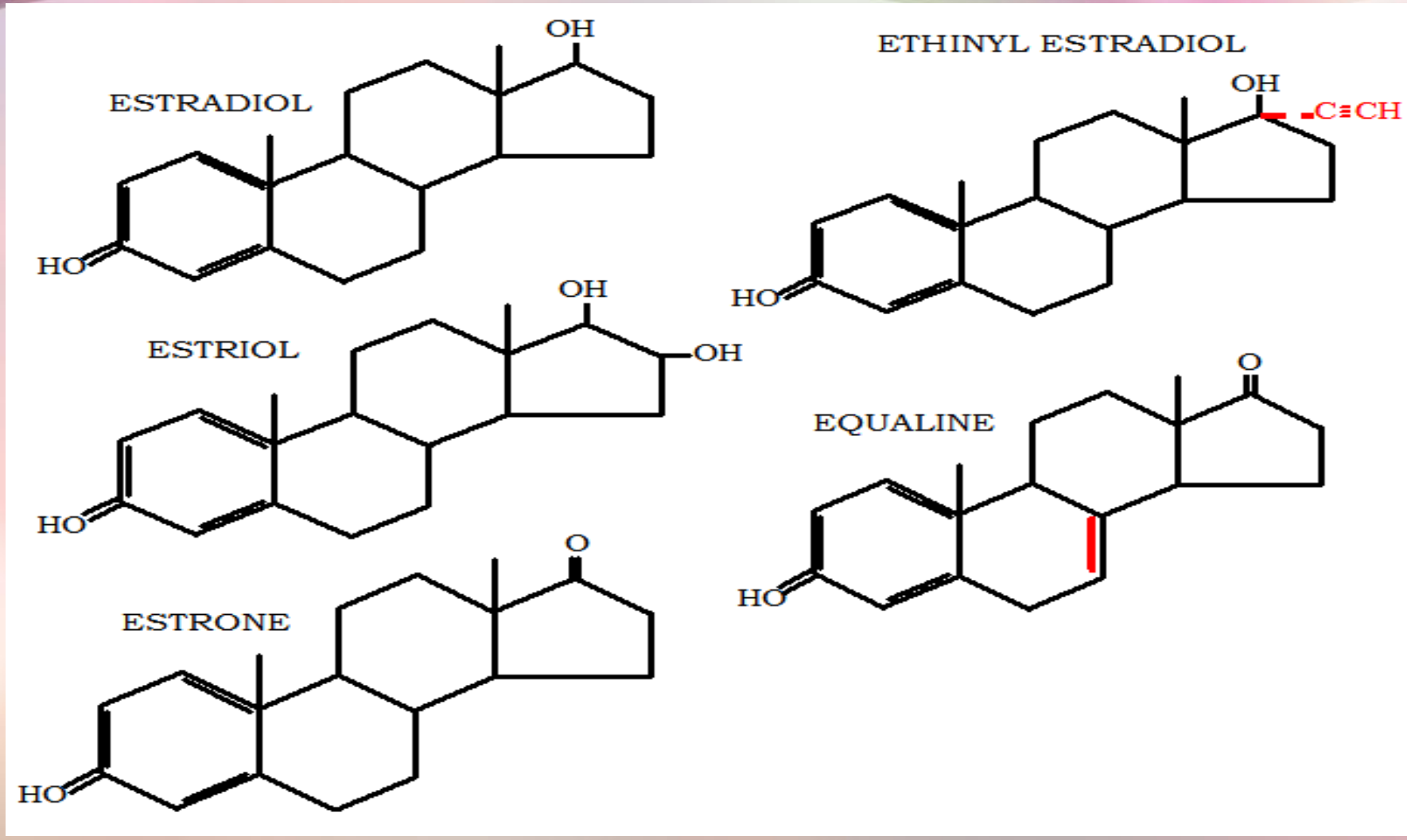
Estrogen(s)



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Natural Vs. Synthetic Estrogen

Natural Estrogen

- Eliminates hot flashes
- Restores mood
- Maintains thickness, fullness of skin and hair
- Maintains genital/pelvic health
- Protects against colon cancer and macular degeneration

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Natural Vs. Synthetic Estrogen

Natural Estrogen

- **Transdermal E2 does not increase risk of VTE like oral E2**
- **Cardioprotective, decreased risk of AMI**
- **Decreased risk of T2DM**
- **Internal Carotid Artery lumen widens by 224% when patient administered Estradiol > 6 months.**

Jonas HA et al, Ann Epidemiol, 1996, 6 (4) : 314-23

Mueck AO. Et al. Postmenopausal hormone replacement therapy and cardiovascular disease: the value of transdermal estradiol and micronized progesterone. Climacteric. 2012 Apr;15 Suppl 1:11-7

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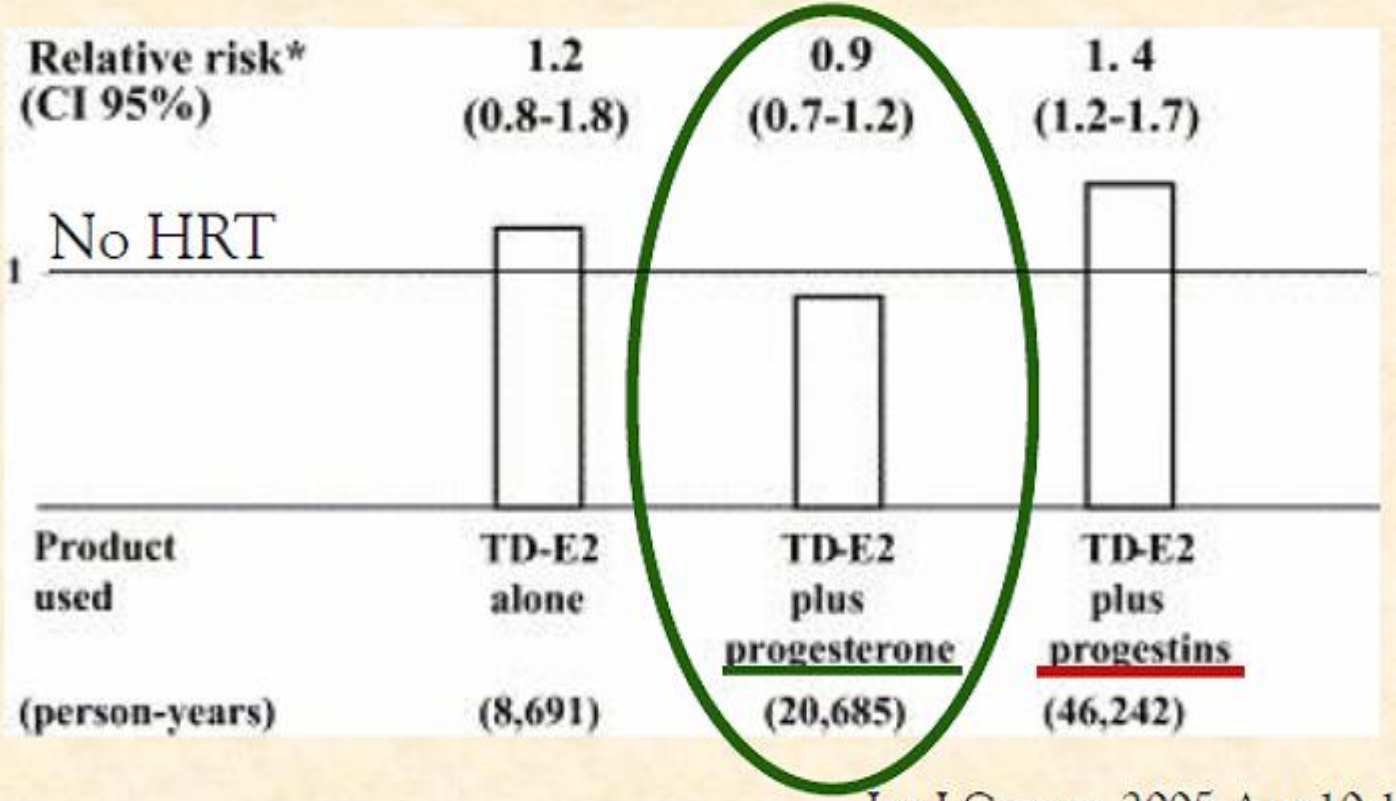
E3N-EPIC Study

Cohort study
55,000 women
8 years f/u
c/w WHI--
16,000, 6 yr. f/u

TD-E2 = transdermal estradiol



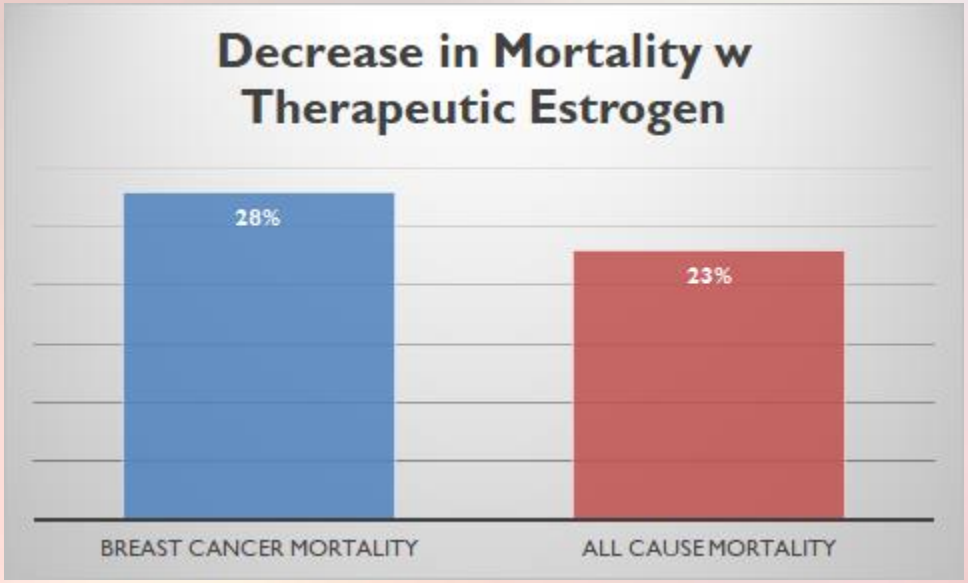
Int J Cancer. 2005 Apr 10;114(3):448-54

E2 plus progesterone: no increased risk of breast cancer!

Similar study: estradiol + progesterone 0.4; estradiol + synthetic progestin 0.94
Espié, Gynecol Endocrinol. 2007 Jul;23(7):391-7.

Natural Vs. Synthetic Estrogen

23, 000 women treated with (Natural) E2/E3 (+/- Progestins)



(1) Schairer C et al. Epidemiology, Jan 1997, Volume 8 Number 1

(2) Batur, P et al. Menopausal Hormone Therapy in Women with Breast CA. Maturitas 53(2006)123-132

(3) Durna, E et al. Breast Cancer in Premenopausal Women: recurrence and survival rates and relationship to hormone replacement therapy. Climacteric 2004;7:284-291.

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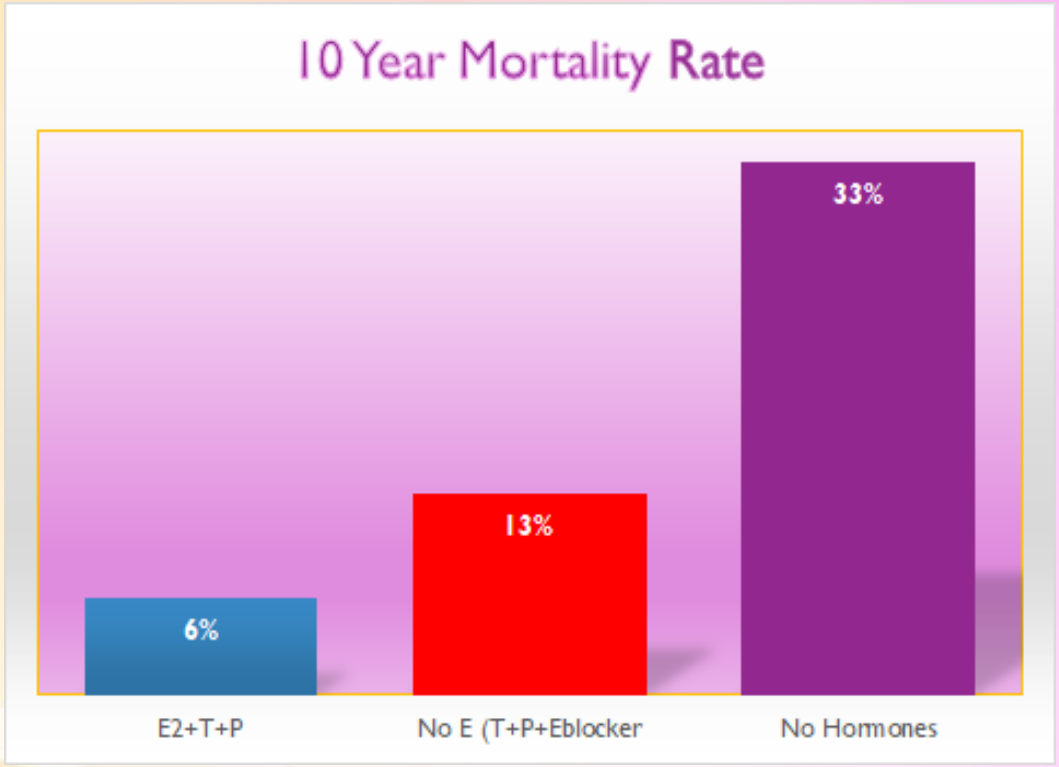
Hormone Replacement After Breast CA

Long Term (Avg 11.6 yr) Survival Rate In Patients Taking Bioidentical E2 Post Breast Cancer



Estrogen replacement does not increase recurrence or mortality. Adding progesterone decreases recurrences.

Natrajan, PK, Soumakis, K., Gambrell, RD Jr. Estrogen replacement in women with previous breast cancer. Am J. Obstet Gynecol. 1999 Aug;181(2):288-95. Atlanta, GA.

Natural Vs. Synthetic Estrogen

Synthetic Estrogen

- Synthetic estrogen increases blood pressure, triglycerides

- Estrone (the cancer causing component of estrogen) causes:
  - Gallstones
  - Elevated liver enzymes
  - Elevated SHBG (decreases testosterone)
  - Interrupts tryptophan and consequently serotonin metabolism
    - Leads to brain fog and depression
    - Lower growth hormone
    - Increases prothrombotic effects,
    - Increases CRP
    - Increases carbohydrate cravings.

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A Brief Word on Progesterone

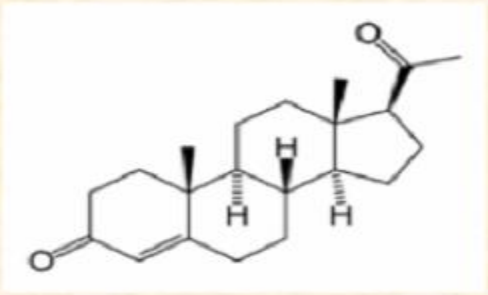
Scientific studies show that:

Provera®	≠	Progesterone
• Causes birth defects		• Maintains pregnancy
• Can cause depression		• Improves mood
• Insomnia, irritability		• Improves sleep
• Fluid retention		• Diuretic
• Raises blood sugar		• No effect on blood sugar
• Counteracts estrogen-induced arterial dilation		• Maintains estrogen-induced arterial dilation
• Worsens lipid profile		• Improves lipid profile
• Causes heart attacks		• No evidence of ↑ CVD
• Increases estrogenic stimulation of breasts		• Reduces estrogenic stimulation of breasts
• Causes breast cancer		• Prevents breast cancer

A Brief Word on Progesterone

Progestins ≠ Progesterone

Progesterone ≠ Medroxyprogesterone Drospirenone



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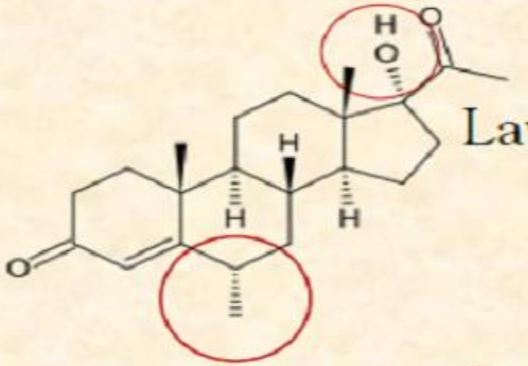
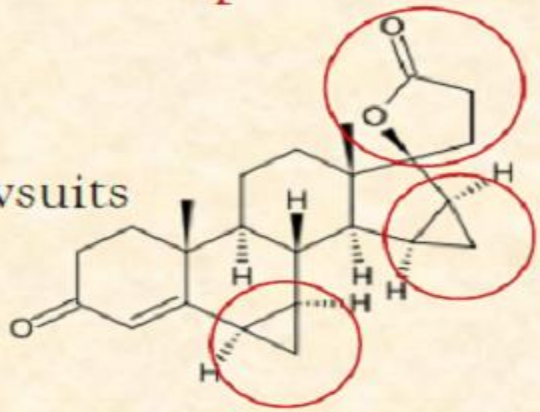


Provera® Prempro®

Lawsuits



Yasmin®

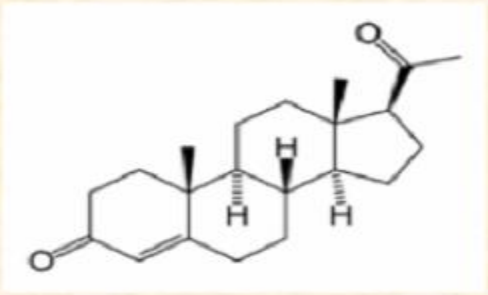
Confusion:

Progestins are often called "progesterone", in the media and in scientific papers!

A Brief Word on Progesterone

Progestins ≠ Progesterone

Progesterone ≠ Medroxyprogesterone Drospirenone



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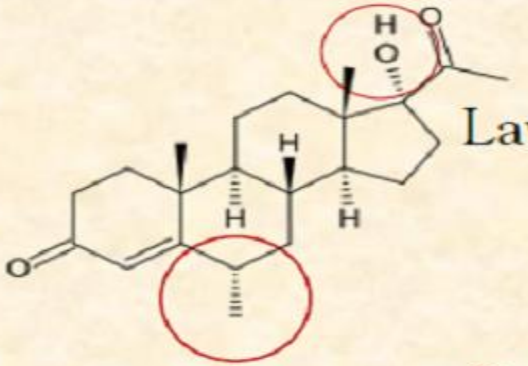
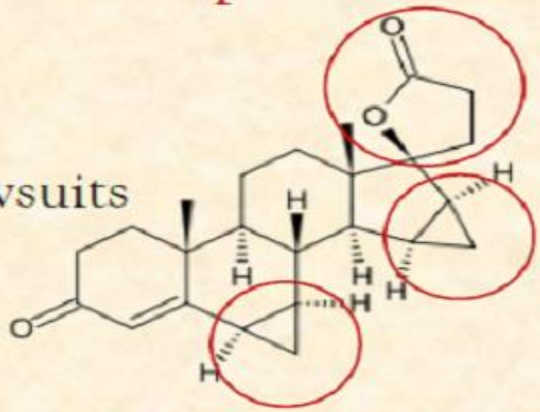


Provera® Prempro®

Lawsuits



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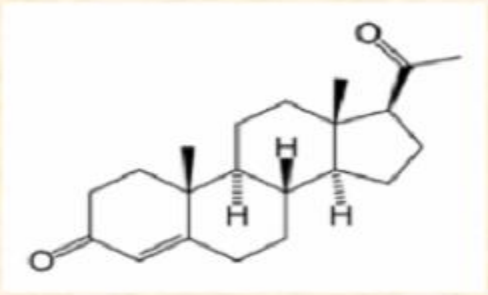

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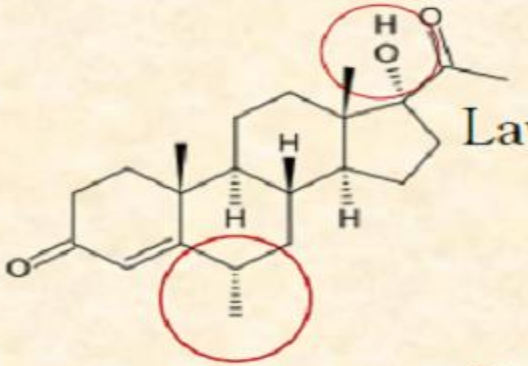
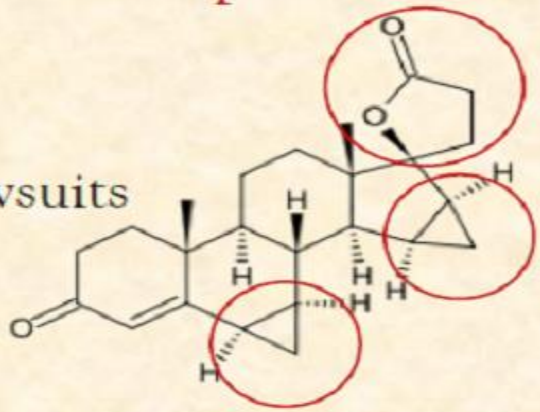


Provera® Prempro®

Lawsuits



Yasmin®

Confusion:

Progestins are often called "progesterone", in the media and in scientific papers!

Low Progesterone= ↑ Cancer

722 Patients, 33 year follow up

Dx: Infertility w luteal phase defect and Progesterone Deficiency

10 X ↑ death from all cancer

5.4 X ↑ premenopausal breast cancer

Cowan LD, et al Breast Cancer incidence in women with a history of progesterone deficiency. Am J. Epidemiol. 1981 Aug:114(2);209-17.

Formby B, Wiley TS. Progesterone inhibits growth and induces apoptosis in breast cancer cells: inverse effects on BCl=2 and p53. Am Clin Lab Sci. 1998:28(6)360

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Estrogen, Progesterone and Breast Cancer

Never, Ever, Never, Ever Use Estrogen without Progesterone

Never, Ever

You All Have to Pinky Swear



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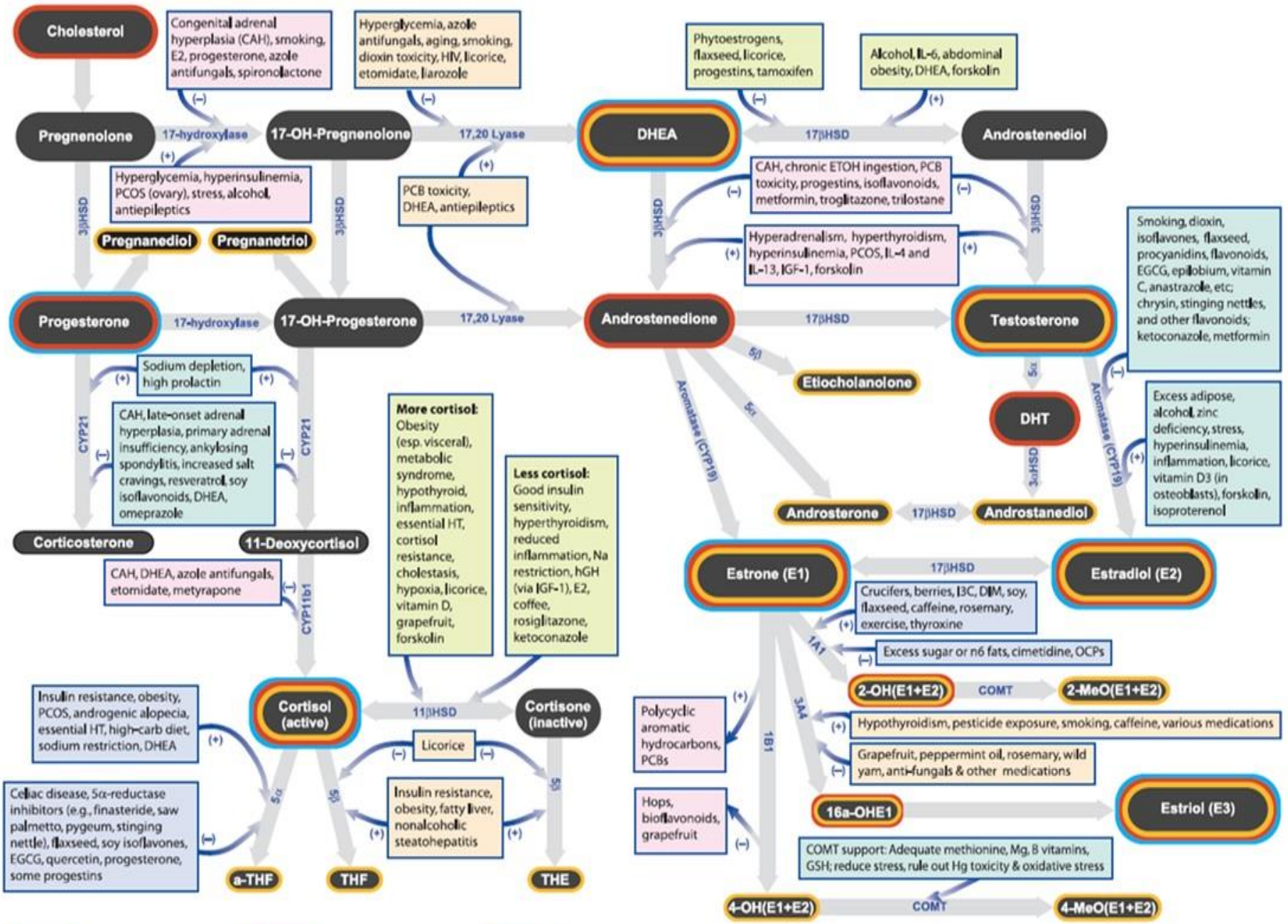
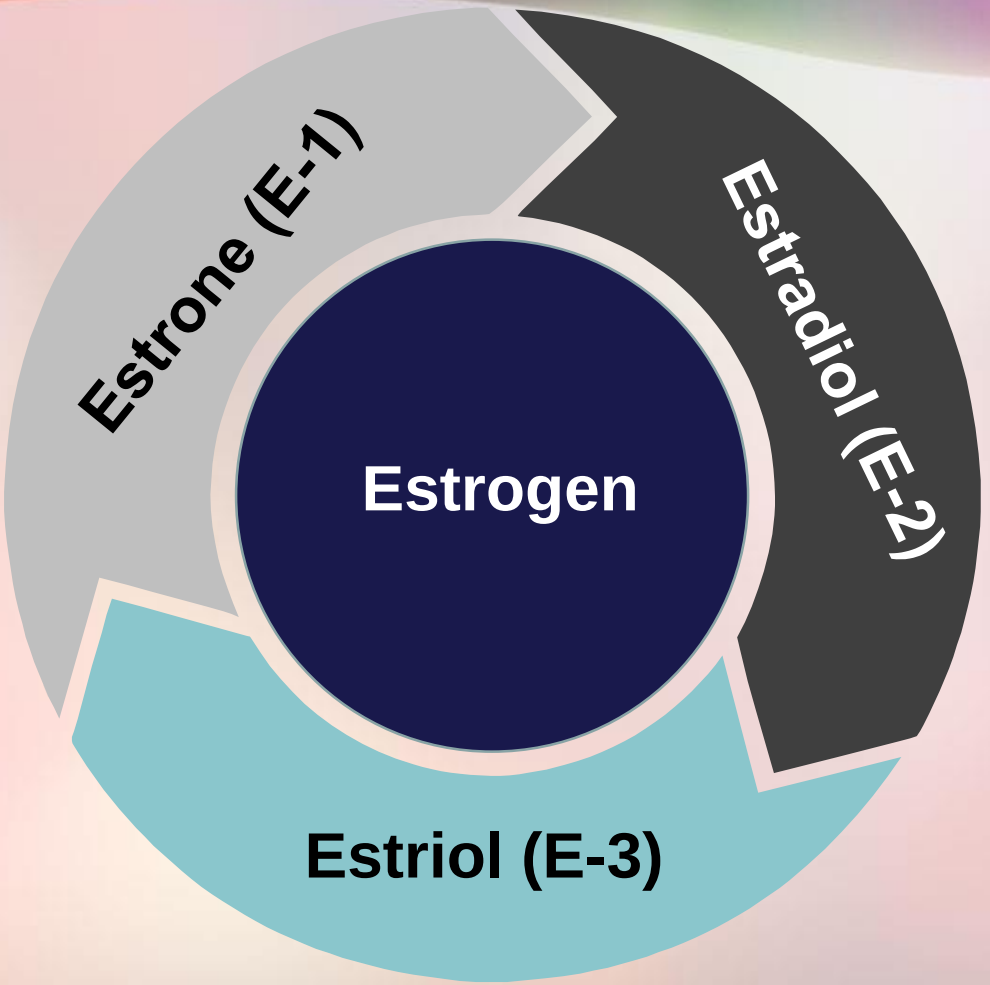
Steroidogenic Pathways



“Natural” Estrogen



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“Natural” Estrogen

3 DISTINCT ESTROGEN MOLECULES

- Estrone (E–1)
- Estradiol (E–2)
- Estriol (E–3)

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"Natural" Estrogen

ESTRONE

- The main estrogen the body makes postmenopausally
  - Produced by adrenal glands and fat tissue
- High levels increase risk of breast cancer

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“Natural” Estrogen

ESTRONE

Increases:

AMI, Stroke, Breast Cancer, Prostate Cancer

Thrombogenic,

Acne

Breakdown Products:

2-OH = “Angel of Mercy”

4-OH, 16-OH = “Angels of Death”

Lower w 7 Keto DHEA

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“Natural” Estrogen

- **Eliminates Hot flashes, restores sleep**
- **Restores Cognitive function and mood**
- **Maintains thickness, fullness of hair and skin**
- **Maintains genital/pelvic health**
  - **Vaginal Lubrication, incontinence and bladder infections**
- **Protects against colon cancer and macular degeneration**

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“Natural” Estrogen

Estradiol

- Increases HDL
- Decreases LDL and total cholesterol
- Decreases triglycerides
- Helps maintain bone structure
- Increases serotonin
- Decreases fatigue
- Works as an antioxidant
- Helps maintain memory
- Helps absorption of calcium, magnesium, zinc

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"Natural" Estrogen

Estriol (E–3)

- Less stimulatory- 80 times weaker than E2
- Protects against breast cancer
- Has no bone, heart, or brain protection of estradiol.

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"Natural" Estrogen

Estriol (E–3)

- Maintains pregnancy
- Maintains vaginal lining
- Occupies the estrogen receptor sites in breast tissue blocking E1
- Controls menopause symptoms
- Increases HDL, Decreases LDL

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"Natural" Estrogen

Estriol (E-3)

- Reduces pathogenic bacteria
- Restores vaginal pH of the vagina
  - Prevents urinary tract infections
- Aids GI tract maintain a favorable environment for the growth of lactobacilli

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Estrogen Receptor Sites

Estrogen Receptor Alpha

- *Increases cell growth*
  - *E1 activates estrogen-receptor alpha selectively in a ratio of 5:1*
    - *Result= Increased cell proliferation*
  - *E2 activates estrogen-receptors alpha (and beta)*

Estrogen Receptor Beta

- *Decreases cell growth*
  - Helps prevent breast cancer development
- *E2 activates estrogen-receptor beta*
- *E3 binds to estrogen-receptor beta in a 3:1 ratio*
  - *E3 aids in breast cancer prevention*

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Estrogen Metabolism

Two Major Pathways:

2-OH estrone

4-OH estrone

One Minor Pathway:

16-OH estrone

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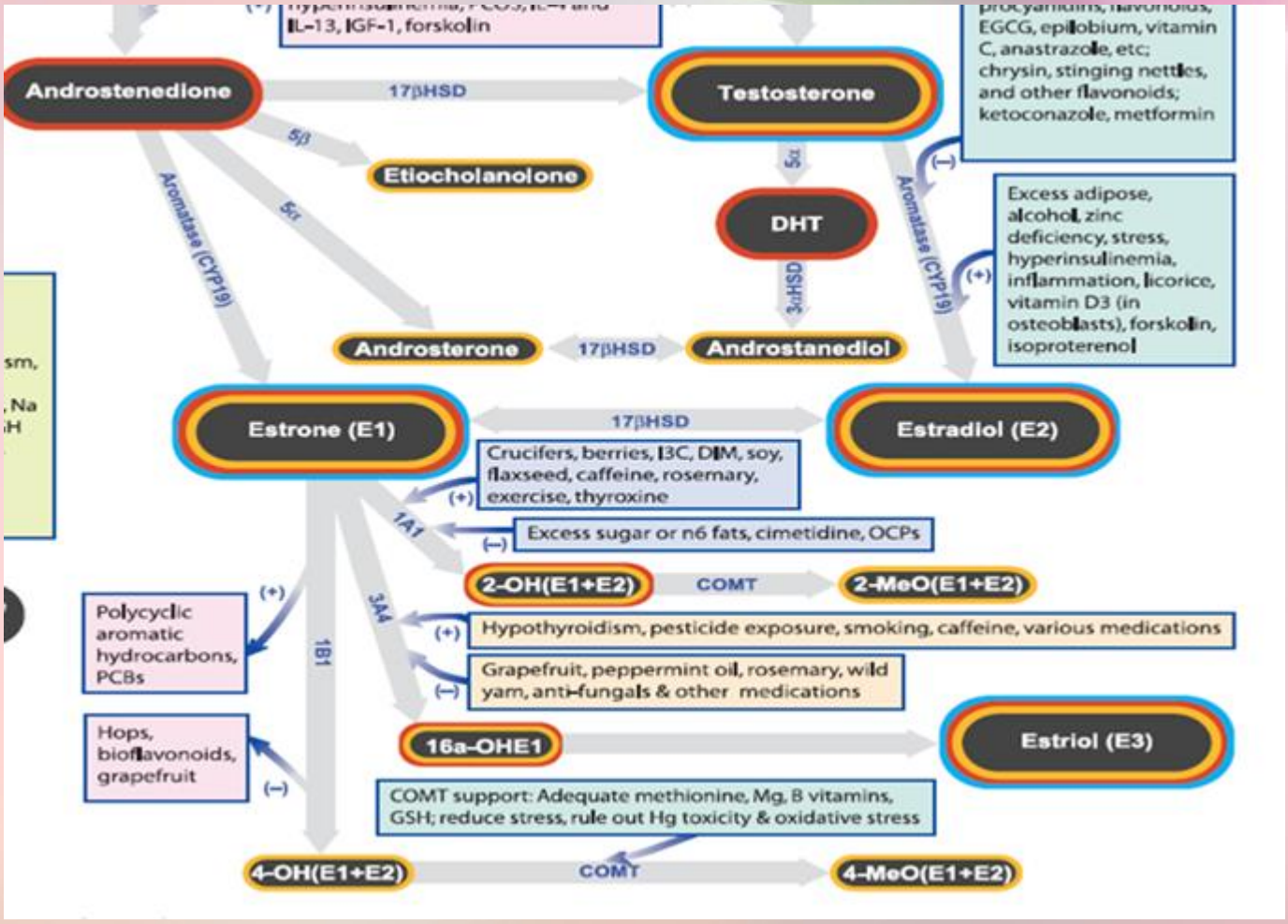
Estrogen Metabolism



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Estrogen Metabolism

2-OH Estrone/Methylation

- ***"Good estrogen."***
  - **Does not stimulate the cell growth.**
  - **Blocks action of carcinogenic estrogen products**

- ***"Protects against cancer"*– methylated by (COMT) into 2-methoxy-estrone.**

- **Urinary 2-methoxyestrone/2-hydroxyestrone**
  - **=methylation ability**

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Estrogen Metabolism

Raising 2–OH Estrone Levels

- Moderate exercise
- Cruciferous vegetables
- Flax
- Soy
- Kudzu
- Broccoli derivatives
  - indole-3-carbinol 200 to 300 mg/day
  - DIM
  - Sulforaphane

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Estrogen Metabolism

Raising 2–OH Estrone Levels

- Omega-3-fatty acids
- B6, B12, and folate
- MTHF
- TMG
- Rosemary, turmeric
- Weight loss
- High protein diet

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Estrogen Metabolism

2-OH Estrone/Methylation

Homocysteine levels are a proxy for methylation

Normal <11 umol/ml Optimal <10 umol/ml

Low ratios of 2/16 OH-estrogen associated with lupus.

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Estrogen Metabolism

Methylation Support

- ***Stress Reduction***
- ***SAMe***
- ***Methionine***
- ***B2, B6, B12***
- ***Folic acid (also as folinic acid, 5–formyl THF, or 5–***
- ***methyltetrahydrofolate––MTHF)***
- ***TMG (betaine)***

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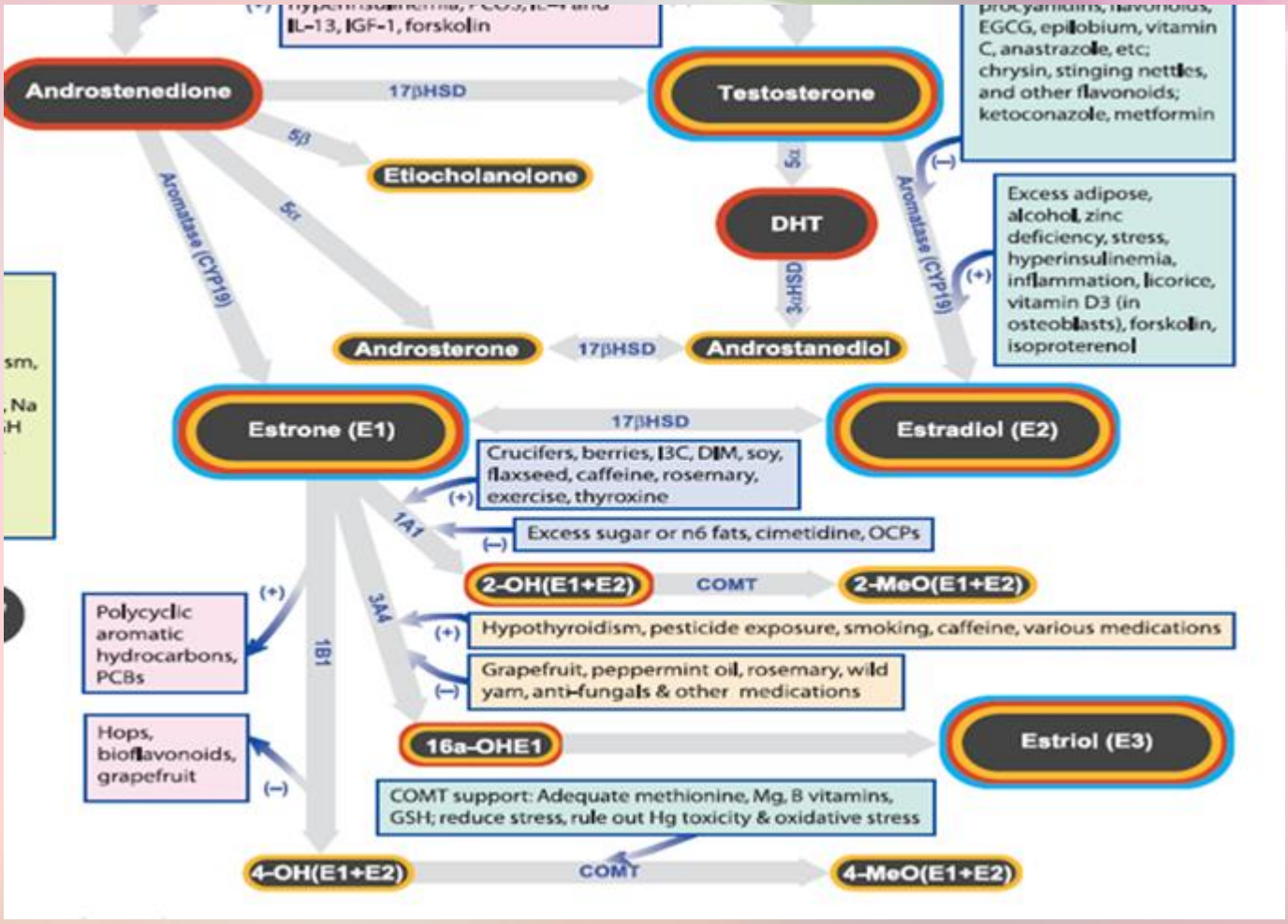
Estrogen Metabolism

16-OH Estrone



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Estrogen Metabolism

16–OH Estrone

- ***Highly estrogenic:***
  - ***Breast cancer.***
  - ***Obesity***
  - ***Hypothyroidism***
  - ***Pesticide toxicity (organochlorines)***
  - ***Omega–6–fatty acid excess***
  - ***Elevated inflammatory cytokines.***

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Estrogen Metabolism

4–OH Estrone

- *Directly damages DNA causing mutations.*
  - *Enhances cancer development.*
- *Equine estrogens metabolize into 4–OH estrone*
- *Increased 4–OH estrone in presence of:*
  - *Methionine deficiency*
  - *Folic acid Deficiency*
  - *Uterine fibroids*

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Estrogen Metabolism

Estrogen Disruptors

- ***Obesity ⇩ 2-OH/16-OH Ratio***

Xenoestrogens

- ***Pesticides***
- ***Synthetic hormones fed to animals***
- ***Plastics***
- ***Cosmetics***

Alcohol

Antibiotics

- ***GI Flora disruption → Leaky Gut → Inflammation***

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Estrogen and the Brain

Estrogen Increases:

- Blood flow
- Glucose and oxygen
- Neurotransmitter quantity and function
- Sensitivity to nerve growth factor
- Manual speed and dexterity
- Availability of acetylcholine
- Long term memory

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Estrogen and the Brain

Decreases:

- **Alzheimer's beta amyloid peptides**
- **Distractibility**

Protects neurons

Keeps blood-brain barrier intact

Is a natural antioxidant

Signals progesterone receptors

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Estrogen and Psychosis

- **Estradiol has properties similar to those of atypical antipsychotic drugs.**
  - **Influences:**
    - **Dopaminergic**
    - **Serotonergic**
    - **Glutamatergic systems**

- **The theory that many serious mental illnesses, specifically schizophrenia, may have a significant hormonal etiological component is fast gaining popularity**
- **and the support of scientific evidence.**

The Role of Estrogen and Other Hormones in the Pathophysiology and Treatment of Schizophrenia Schizophrenia Research and Treatment Volume 2012, Article ID 540273. Emily Hayes, Emorfia Gavrilidis, and Jayashri Kulkarni Monash Alfred Psychiatry Research Centre, The Alfred Hospital and Monash University School of Psychology, Psychiatry and Psychological Medicine, Melbourne, VIC 3004, Australia

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Estrogen and Cognition

- **Estradiol, Testostosterone, and IGF-1 have independent and selective effects on cognition**

Cognitive changes associated with supplementation of testosterone or DHT in mildly hypogonadal men: a preliminary report. J Androl 2003 Jul-Aug;24(4):568-76. Cherrier MM; Craft S; Matsumoto AH Department of Psychiatry and Behavioral Sciences, University of Washington Medical School, Seattle, Washington 98108, USA.

- **17-alpha-estradiol is found to be neuroprotective, after an ischemic stroke and oxidative stress, and in Alzheimer's disease; and influences spatial memory and Hippocampal-dependent synaptic plasticity.**

17-alpha-estradiol: a brain-active estrogen? Endocrinology 2005 Sep;146(9):3843-50. Toran-Allerand CD; et al. Department of Anatomy and Cell Biology, Columbia University College of Physicians and Surgeons, 650 West 168th Street, Black Building, Room 1615, New York, New York 10032, USA

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Estrogen and TBI

- **"Pre-existing" low estrogen levels leave women susceptible to the development PTSD. Conversely, high estrogen levels may be protective.**

- **Estrogen:**
  - **Lowers risk of PTSD after trauma. Is Neuroprotective.**
  - **Modulates pain.**
  - **Strongest predictor of acute mortality and poor long-term outcome.**
  - **CSF estradiol is lower after TBI**

Nauert PhD, R. (2017). Estrogen Levels Influence Susceptibility to PTSD. *Psych Central*. Retrieved on June 26, 2017, from https://psychcentral.com/news/2017/01/20/estrogen-levels-influence-susceptibility-to-ptsd/115390.html

Dr. Seeman, Clarke Psychopathology in Women and Men: Focus on Female Hormones Am J Psychiatry, Toronto, Canada 1997; 154:1641–1647.

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Estrogen and TBI

Estrogen:

- **Maintains cerebral blood flow, lactate production**
- **Prevents apoptosis (cell death), and acts like a growth factor.**
- **Increases under stressful conditions such as critical illness and trauma.**
- ***Decreases risk, onset and progression of neurological deterioration***
  - ***Alzheimer's Disease, schizophrenia***
  - ***Aids in recovering from stroke and TBI.***
- **Prevents neuronal loss in CNS**

- Nauert PhD, R. (2017). Estrogen Levels Influence Susceptibility to PTSD. *Psych Central*. Retrieved on June 26, 2017, from https://psychcentral.com/news/2017/01/20/estrogen-levels-influence-susceptibility-to-ptsd/115390.html

Dr. Seeman, Clarke Psychopathology in Women and Men: Focus on Female Hormones Am J Psychiatry, Toronto, Canada 1997; 154:1641–1647.

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Menopause: Estrogen Deficiency

Hot flashes
Night sweats
Vaginal Dryness
Decreased libido
Memory Loss
Brain Fog
Decreased concentration
Psych Issues:
Loss of Femininity
Fear of Aging

Dementia
Fatigue, Low energy
Depressed mood
Stress incontinence/ UTI's
Osteoporosis
Cardiovascular disease
Cerebrovascular Dx.

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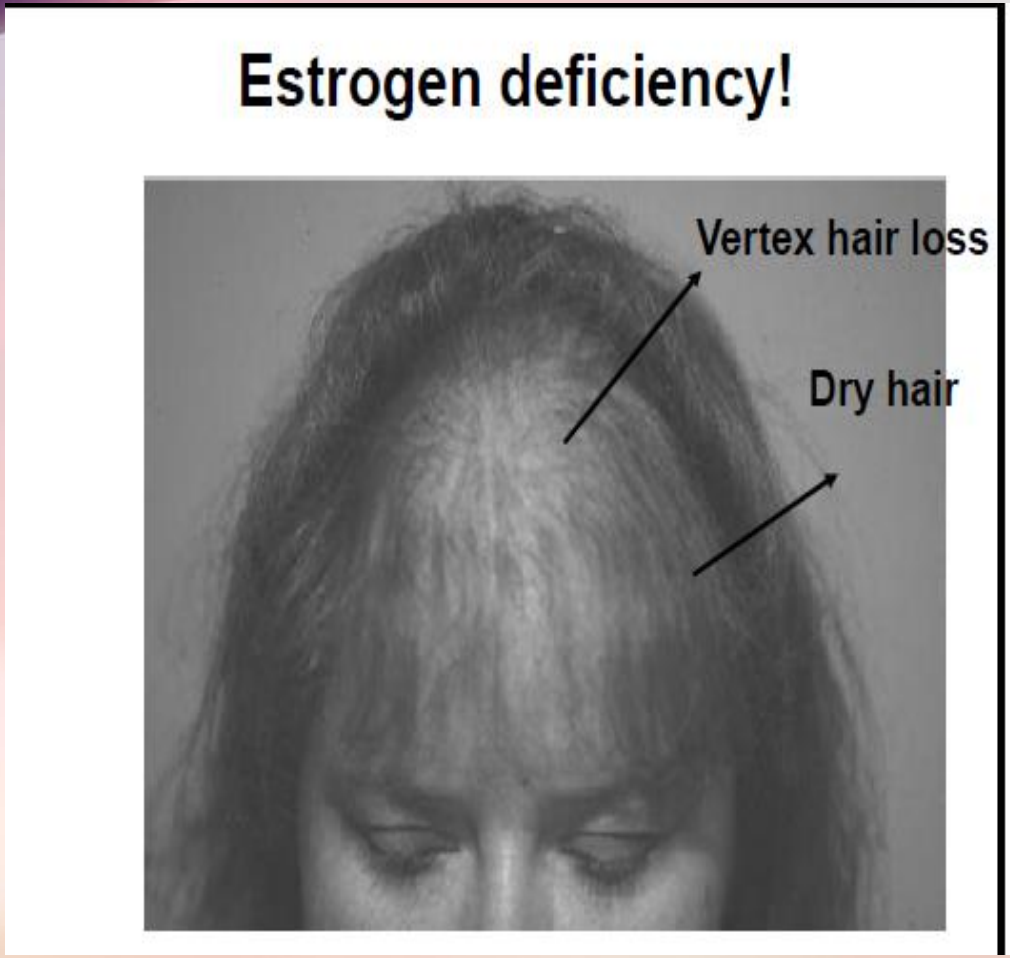
Estrogen Deficiency:Physical S/S





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Estrogen Deficiency:Physical S/S

Mucosal Wasting (Vaginal Atrophy)

Decrease in Lean Mass

Increase Fat Mass

Thinning Hair, Flat Scalp Hair

Loss of Hair on Vertex

Poor Hair Volume

Loss of Height (0.22 cm/yr)

Maxillofacial inflammation-Jawbone receding

Headaches, Fatigue during menses

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Estrogen Dominance

- Effect of too much estrogen relative to progesterone
- Frequently seen in women of all ages
- Effects of xenoestrogens
- Parabens, phthalates, BPA
- Progesterone deficiency
- Progesterone resistance!
- Common Denominator:

Estrogen Dominance=Inflammation

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S/S Estrogen Dominance
Think "Cysts"

Allergies

- Anxiety
- *Autoimmune disorders*
- *Breast cancer*
- *Breast tenderness*
- Cervical dysplasia
- Cold hands and feet
- Decreased sex drive
- Depression
- Dry eyes
-

Early onset of menstruation

- *Endometrial cancer*
- *Fat in hips/thighs*
- *Fatigue*
- *Fibrocystic breasts*
- *Gallbladder disease*
- Headaches
- Hypoglycemia
- Increased blood clotting

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S/S Estrogen Dominance
Think "Cysts"

Infertility

Irregular menses

Irritability

Insomnia

Mg deficiency

Mood swings

PCOS

Osteopenia/osteoporosis

PMS

Sluggish metabolism

Thyroid dysfunction

Uterine cancer

Uterine fibroids

Water retention/bloating

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S/S Estrogen Dominance Etiology

↑ Aromatase = ↑ Estrogen

Obesity= ↑ levels of aromatase breast tissue

Inflames WAT (white adipose tissue) = Inflammation

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Biochemistry of Estrogen Dominance



WAT = PGE2 Expression =



COX 2 =CYP 19 transcription



aromatase activation= Estrogen Production

Subbaramaiah, et al. Cancer Discov. 2012 Apr;2(4):356-65

Increased pro-inflammatory mediators= Inc. NF-kB =

Elevated induction of aromatase = Lipolysis = Inc. FFA =

Increased TNF a, IL-1, PGE2 to turn on aromatase

Subbaramaiah, et al (Cornell). Cancer Prev Res. Sep, 2013.

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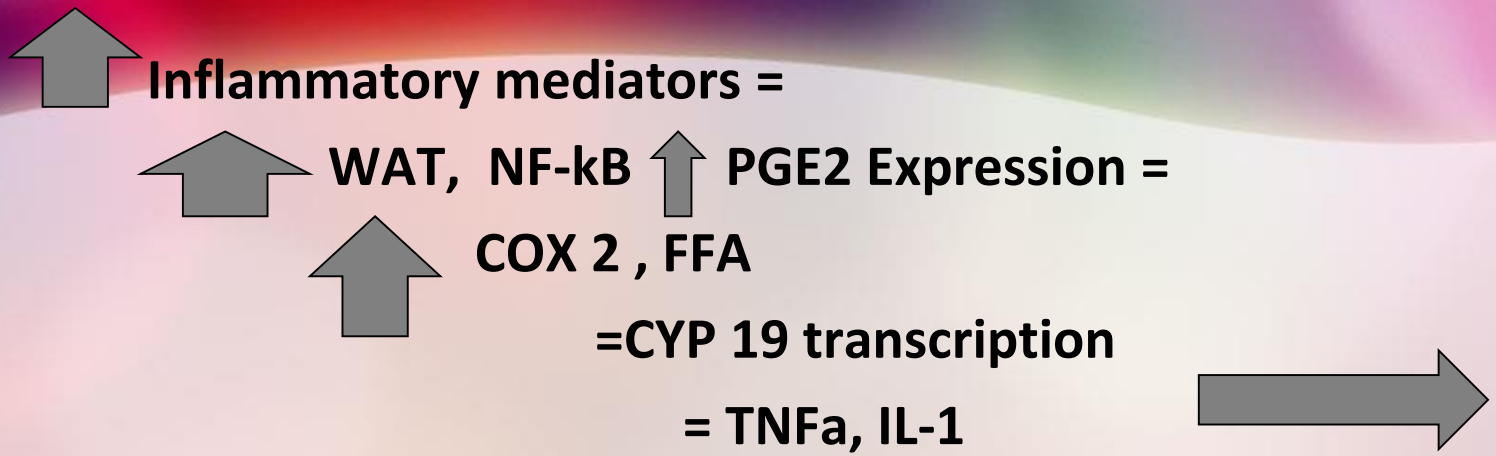
Biochemistry of Estrogen Dominance



Subbaramaiah, et al. Cancer Discov. 2012 Apr;2(4):356-65

Subbaramaiah, et al (Cornell). Cancer Prev Res. Sep, 2013.

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Endocrine Disruptors

BPA found in 92% of US Men and Women

BPA Induces Cox-2 Expression

BPA affects methylation

Increases prostate and breast cancer risk

BPA exposure associated with:

- **Recurrent miscarriages**
- **Endometrial hyperplasia**
- **PCOS**
- **ADHD**
- **Fibroids**
- **Sexual dysfunction**
- **Breast Cancer**
- **Inc. 4-OH/2 OH Metabolism = *Inflammation***

Wang, et al. Taiwan J Obstet Gynecol. June 2013.

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Estrogen/Progesterone Balance



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Estrogen/Progesterone Balance

Estrogen	*Progesterone*
Good Energy/Mood	***Calming***
Low Energy/Mood	***Nervous***
Passive	***Irritable (Before Menses)***
Fatigued-during menses	***Agitated***
Depressed-@ menses	***Anxiety***
Menstrual Headache	***Headaches before menses***
Poor Libido	***Excessive, nervous libido***

S/S During Menses

S/S Prior to Menses

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Physical Appearance

Estrogen

Water Retention

- *Tired*
- *Water Excretion*
- *Irregular Menses*
- *Amen-Hypomenorrhea*
- *Breast Droop*
- *Episodic dysmenorrhea*
- *Vaginal Dryness*

Progesterone

Water Excretion

- *Nervous*
- *Water Retention (Swelling)*
- *Menorrhagia*
- *Weight Gain*
- *Swollen Breasts*
- *Constant dysmenorrhea*
- *Excessive Lubrication*

S/S During Menses

S/S Prior to Menses

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Deficiency Comparison

Estrogen Deficiency

Water Retention

Tired Appearance

Pale

Wrinkles

Facial Hollows

Vaginal Dryness

Thin body type

Abdomen Deflated

Rheumatoid Dx.

Osteoporosis

CV Dx.

Progesterone Deficient

Water Excretion

Nervous, Tense Appearance

Red in Face

Weight Gain

Facial Swelling

Excessive Lubrication

"Obese" body type

Abdomen swollen

Cysts +/- CAncer:

Breast, Ovarian, Fibroids

S/S During Menses

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Estrogen Laboratory Tests

- **Hormone ranges are based upon pooled data.**
- **Usually a two standard deviations a randomized mean defines the range.**
- **Hormone levels should be centered around the median level of its acceptable range.**
- **The ideal net effect is that the levels are close to the median of the range**
- **Ranges may be narrow; i.e.**
  - **Post-menopausal Progesterone (0.1-0.8 ng/ml)**

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Lab Studies

Central	*Peripheral*
TSH	**free T3, free T4, reverse T3, TPO, anti thyroglobulin**
GH	**IGF-1, IGFBP3**
LH/FSH	**Testosterone, (free, total), DHEA-S** **Male-DHT, Estradiol** **Female-Estrone, Estradiol, Progesterone**
ACTH	**Cortisol A.M. and P.M. or 4 Point Cortisol Saliva Test**
Others	**CBC, Chem Profile, Lipid Profile, cRP, Homocysteine, Insulin, 25-OH Vit D, Pregnenolone, PSA (Total and fractionated), Zinc, Prolactin**

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Lab Studies

Estrone	<30 pg/mL	<100 pg/mL	M (<60) F (<100)
Estradiol	<25 pg/ml	90 pg/ml	M (7.6-42.6) F (<54) Postmenopausal
Progesterone	0.8ng/ml	5-7 ng/m	M (0.2-1.4) F (0.1-0.8) postmeno.

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Laboratory Target Ranges

Hormone	Median Male	Median Female	Range
Estrone	<30 pg/mL	<100 pg/mL	M (<60) F (<100)
Estradiol	<25 pg/ml	90 pg/ml	M (7.6-42.6) F (<54) Postmenopausal
Progesterone	0.8ng/ml	5-7 ng/m	M (0.2-1.4) F (0.1-0.8) postmeno.
Pregnenolone	<194 ng/dL	<205 ng/dL	M (38-350) F (250-500)
Vitamin D 3	>60 ng/ml	>60 ng/dL	M (30-100) F (30-100)

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Laboratory Target Ranges

Hormone	Median Male	Median Female	Range
LH	5.1 mIU/mL	6.2 mIU/ml (Day 21 or postmenopausal)	M (1.7-8.6) F (Phase Dependent)
FSH	6.95 mIU/ml	8.6 mIU/ml	M (1.5-12.4 mIU/ml) F (Phase dependent)
Prolactin	11.25 ng/ml	13.75 ng/ml	M (2.5-19) F (2.5-19)

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Disease Risk within E2 Reference Range

Serum E2	Lab Values	Disease RIsk
Pre-menopause-"normal"	100-110	Osteoporosis
E2 (Day 7 of Cycle)	<97	Cardiovasc. Dx.
	<81	Dec. Bone Density Cyclical Migraine
	<60	Coronary artery constriction
Menopausal	<54	Psychosis
	<50	Postpartum Depression
	<38 pg/ml	Ischemic Heart Dx

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Estrogen/Progesterone Ratio

- **Optimal time to perform lab testing is days 19-21**

- **Measuring both Estrone (E1) and Estradiol (E2) with progesterone (PROG) will allow for the calculation of the EP Ratio.**

E1+E2/P=E/P Ratio

- **Estrogen Dominance as a comorbid factor to TBI can cause greater disturbance in neurochemistry especially with GABA.**

- **If E1 is elevated, control w 7 Keto-DHEA**

Gordon, M., Traumatic Brain Injury, Millennium Health Centers, 2015, San Diego, CA. 143-144

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Estrogen/Progesterone Ratio

(Gordon, M. TBI, San Diego, 2015)

Symptoms	*<250*	*250-1000*	*1000-5000*	*>5000*
Headaches	Intermittent	Mild	Moderate	Severe
Sleep Issues	Intermittent	Mild	Moderate	Severe
Sleep Deprivation	NP	Intermittent	Mild	Moderate
Bloating	NP	NP	Mild	Moderate
Mood Swings	NP	Mild	Moderate	Severe
Anxiety	NP	Intermittent	Mild	Severe
Depression	NP	Intermittent	Mild	Severe
Panic Attacks	NP	Intermittent	Mild	Severe
Mastalgia	Intermittent	Mild	Severe	Severe

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Progesterone/Estradiol Ratio

- **Alternative Measurement**
  - ***Serum: Pg x 1000/E_2=P/E_2 Ratio***
  - ***Saliva: Pg/E_2=Pg/E_2 Ratio***
- **Results**

<100	**=**	**Estrogen Dominant**
100-500	**=**	**Normal Ratio**
>500	**=**	**Progesterone Dominant**

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Marie R:

BP 108/68 Pulse 80 I Temp (Src) 98.7 (Tympanic) I Resp 181 Ht 5' 3.7" (1.618m) I Wt. 215 lbs 14.4 oz (97.932kg) I BMI 37.41 kg/m2 I BSA 2.1 m2 I Sa0 2 97[room air[%

PE: General: Normotensive, in no acute distress.

Eyes: PERRLA, EOMI full, conjunctiva clear, eyebrows nearly absent

Neuro: Hyporeflexic biceps, patellar

Vaginal atrophy, some evidence of lichen sclerosis

2/26/17	*Marie*	*Median*			*Marie*
Median					
Testosterone Free	1.3 pg/ml	2-4 pg/ml*	TSH	4.30	<2.5
Testosterone Total	19.0 ng/ml	<44 ng/ml*	free T3	1.9	>2.5
DHEA-S	77 ug/dl	195 ug/dl*	free T4	1.42	>1.5
Estrone (E1)	42 pg/ml	< 200 pg/ml*	rT3	328	80-250
Estradiol (E2)	<0.5 pg/ml	90 pg/ml*	T3/rT3	0.58	>1.06
Progesterone	0.10 ng/ml	5-7 ng/ml*	TPO	462	<35
Pregnenolone	108 ng/dl	100 ng/dl*	TAG	179	113
EP Ratio	420	< 250			
P/E Ratio	inf	100-500			

Other: 25 OH D 41 Homocysteine 14.2 Hct 37.5, cRP 2.07, Insulin 15, FBS 101

Julia R.

Irregular Periods, Heavy Bleeding

Hormone	Result	Median
Estrone (E-1)	274	<200 pg/ml
Estradiol (E-2)	191	90 pg/ml
Progesterone	0.06	5-7 ng/ml
Pregnenolone	66	100 ng/dL
EP Ratio	7750	<250
P/E Ratio	0.22	100-500

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Julia R.

Female Hormone Testing	Results	Range
Growth Hormone	1.6	5ng/ml*
Somatomedin C (IGF-1)	128	> 200 ng/ml
IGFBP-3	3100	>4000 ng/ml
DHEA-S	49.2	195 ug/dl*
Estrone (E1)	**274**	**< 200 pg/ml***
Estradiol (E2)	**191**	**90 pg/ml***
Progesterone	**.06**	**5-7 ng/ml***
Pregnenolone	**66**	**100 ng/dl***
EP Ratio	**7750**	**< 250**

DHT	23	< 30ng/Dl
SHBG	88	< 75 pg/ml
FSH	6.8	7 mIU/ml*
LH	5.0	5.1mIU/ml
Prolactin	7.2	14 ng/ml*
Zinc	89	95mcg/dL
Insulin	8	<30mIU/L
Vitamin D3	17	>60 ng/dl*
ACTH	16	35 pg/ml *
Cortisol	18.9	< 15 ug/dl

Testosterone Free	0.8	2-4 pg/ml*
Testosterone Total	12.7	<44 ng/ml*

TSH	0.98	<2.5 mcu/ml*
T3, Free	3.6	> 2.5 pg/ml
T4, Free	1.8	> 1.5 ng/ml
rT3	168	80-250 pg/ml
T3/rT3 Ratio	2.14	>1.06
TPO	19	<35

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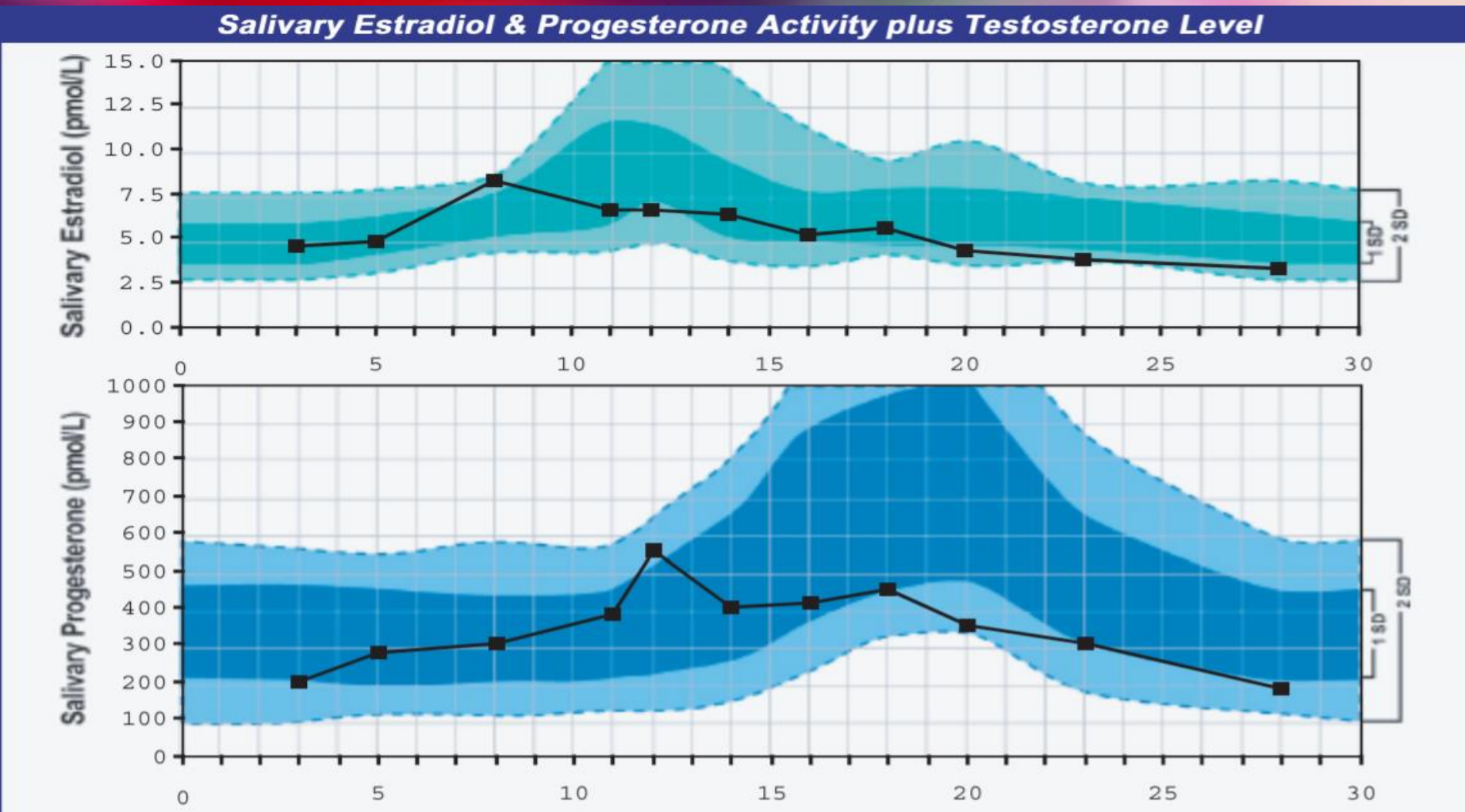
Normal 28 Day Saliva Test-Perimenopause



Day of Cycle	3	5	8	11	12	14	16	18	20	23	28	Avg.
Estradiol	4.5	4.8	8.2	6.5	6.5	6.3	5.2	5.5	4.3	3.8	3.2	5
Progesterone	200	280	300	380	550	398	412	450	350	300	180	345
P/E2 Ratio	44	58	37	58	85	63	79	82	81	79	56	66

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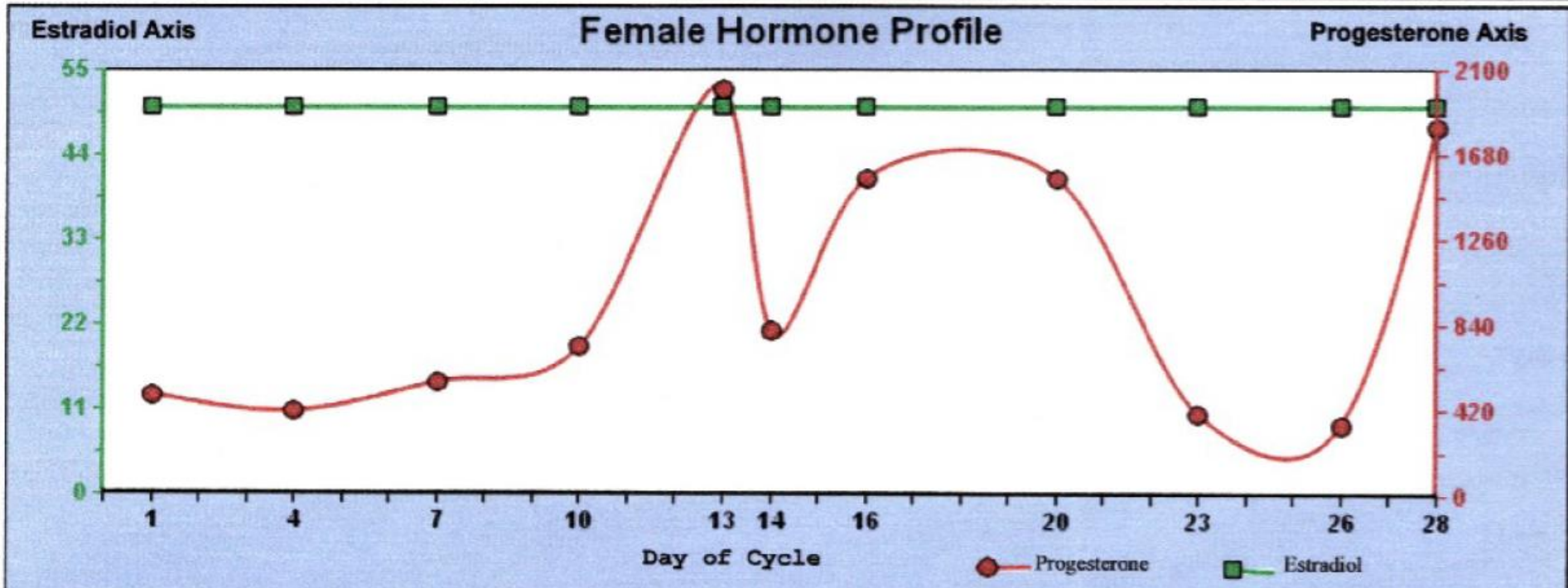
Julia's 28 Day Saliva Test-Perimenopause

FHP **Pre Menopause Female Hormone Panel - Saliva**

Day of Cycle	Day	1	4	7	10	13	14	16	20	23	26	28
Estradiol	pg/ml	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50
Progesterone	pg/ml	491	409	553	728	>2000	809	1557	1557	394	348	1814

Cycle Information		
	Start	12/20/2017
	End	01/16/2018
	Length	27

Ranges	*Phase*	*Estradiol*	*Progesterone*
	Follicular	2 - 10 pg/ml	20 - 100 pg/ml
	Preovulatory	**7 - 25 pg/ml**	
	Luteal	3 - 16 pg/ml	65 - 500 pg/ml



28 Day Saliva Test-Perimenopause

28-Day Saliva Test Estradiol Norms

- **Follicular: 2.8–8.8 pmol/L**
- **Peak: 4.5–19.1 pmol/L**
- **Luteal: 2.8–8.2 pmol/L**
- **Menopausal: 3.7–9.4 pmol/L**

28-Day Saliva Test Progesterone Norms

- **Follicular: 120–593 pmol/L**
- **Peak: 328–1385 pmol/L**
- **Luteal: 145–797 pmol/L**
- **Menopausal: 163–669 pmol/L**

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Estrogen Therapy

Prescribe Oral Estrogen Under Duress Only

Oral Estrogen Increases:

- **Blood Pressure**
- **Triglycerides**
- **E-1**
- **Liver Enzymes**
- **SHBG**
- **Prothrombotic Effects**
- **CHO Cravings**
- **CRP**

Decreases: Testosterone

- **Growth Hormone**
- **Tryptophan metabolism and Serotonin metabolism**

Cause gallstones

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Estrogen Therapy

More genotoxic estradiol metabolites w/ oral estradiol

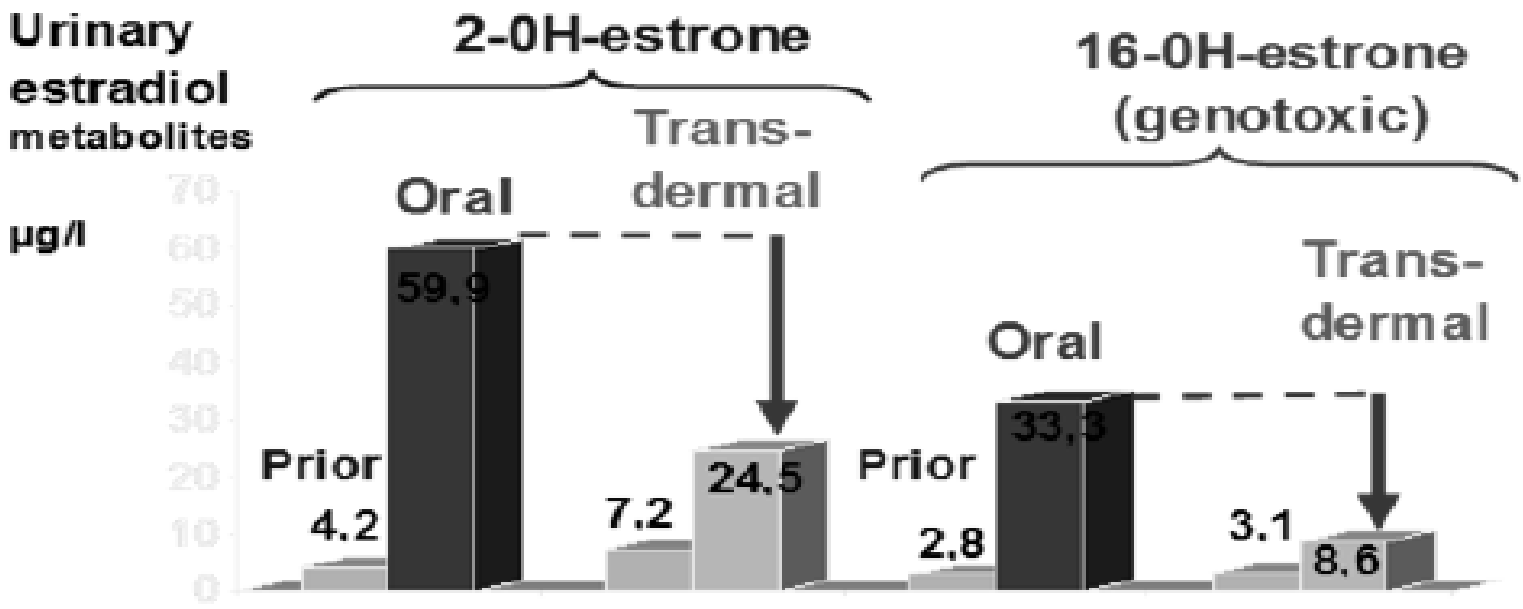

Figure: Les estrogenic metabolites (esp. the genotoxic 16 –OH –estrone) w/ transdermal estradiol.

Seeger et al. 2000

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Pre-menopause Remedies

Low Estrogen=PCOS (Check FBS, HbA1c, Insulin, Testosterone)

1. ***Diet***
   a. ***Low GI, Minifast w Bone Broth, HFLC***
2. ***Insulin Sensitization***
   a. ***Cinnamon-500 mg/d***
   b. ***Chromium picolinate-1200-1600 mcg/d***
   c. ***Alpha lipoic acid 300 mg 1/d (2x/d w neuropathy)***
   d. ***Berberine 200 mg 2x/d (Effective w ⇧ lipids)***
3. ***High Testosterone***
   a. ***Saw Palmetto 240-260 mg/d***
   b. ***Metformin 500 mg 1-4x/d***
   c. ***Spironolactone 50-100 mg/d***

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Estrogen Dominance Rx.

1. Progesterone Days 14-25

2. Lifestyle Changes
    1. Avoid EDC's
    2. Paleo, Anti-inflammatory Diet
    3. Exercise

3. Green Tea

4. Aromatase Inhibition
    1. Quercetin
    2. Glycyrrhiza – licorice
    3. Grape seed extracts
    4. Resveratrol
    5. Anastrozole 1 mg/d x 12 weeks
        1. Reduced fibroid, uterine size, endometriosis 32% in 12 weeks
            1. Hilario et al. Fertil Steril Jan 2009.
            2. Verma and Konje. Eur J Obstet Gynecol Reprod Biol. April 2009

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Estrogen Dominance Rx.

6. Resveratrol
7. Cruciferous Vegetables
8. I3C 200mg/ DIM 100 mg 2x/d
9. Omega 3 FA 1000 mg bid
10. Curcumin 500 mg 1-4x/d
11. Moderate Etoh, Caffeine consumption
12. Evening Primrose Oil

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Fixing Julia

1. Diet
    1. Moderate Caffeine, Alcohol
    2. No white flour, white sugar

2. Estrogen Dominance
    1. Progesterone 5 % Cream 1 gm daily or
    2. Progesterone Micronized 100-200 mg @ bedtime
       Nites 14-25 of cycle for 3 cycles, the reassess
    3. 7 Keto DHEA 25 mg
    4. DIM 1 gm/d inc. by 1 gm/d to 3 gm/d if tolerated
    5. Berberine 1/d
    6. Fish Oil 1000 mg 2/d

Other

cRP	5.71	(normal 0-3, goal <1.0);	Fish Oil 1000 mg bid; Curcumin 500 mg 1-2 bid
25 OH D3	17	(normal 30-100, goal 50-80)	Vitamin D3 6000 IU @ bedtime
Homocysteine	10.8	(normal <11, goal <10)	Methylated, B12, Folic Acid
IGF-1	128	(Goal 200-250)	Secretagogue @ hs or Semorealan 0.2 cc sq

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Female Hormone Treatment (Gordon, M. TBI, San Diego, 2015)

	Estradiol	Estriol	Progesterone	Testosterone	Application
Starter	0.2mg	2.0 mg	100 mg	1 mg	Vaginal
Breast Tender	0.1 mg	2.0 mg	100 mg.	1 mg	Vaginal
Fatigue	0.2 mg	2.0 mg	50 mg.	1 mg	Vaginal
Libido	0.2 mg	2.0 mg	100 mg.	2 mg	Transdermal
Basic	0.2 mg	2.0 mg	100 mg.	No	Transdermal
Breast	0.1 mg	2.0 mg	100 mg.	No	Vaginal
Cancer	none	2.0 mg	100 mg.	1-2 mg.	Vaginal

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Transdermal Progesterone

Progesterone Apply @ Bedtime Nites 14-25

Salivary Lab Value	Progesterone Cream	Progesterone E4M Cap
328-450 pmol/L	25-30 mg	200-250 mg
450-700 pmol/L	20-25 mg	140-200 mg
700-900 pmol/L	15-20 mg	120-150 mg
900-1000 pmol	5-10 mg	90-120 mg
1000-1385 pmol	None	None

Herbal Remedy -Chasteberry or Swedish Sunflower Oil Derivative

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1 Day Saliva Test-Menopause

Estrone **4.7–18.9 pmol/L**

Estradiol

- **Follicular: 2.8–8.8 pmol/L**
- **Peak: 4.5–19.1 pmol/L**
- **Luteal: 2.8–8.2 pmol/L**
- **Menopausal: 3.7–9.4 pmol/L**

Estriol **<133 pmol/L**

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1 Day Saliva Test-Menopause

Treatment

1. **Bi-estrogen cream (80% E3:20% E2) 0.25–2.0 mg daily qd**
2. **Progesterone cream 20 to 30 mg qd OR**

2A. Progesterone Capsule 25 to 150 mg E4M

3. **Testosterone cream 0.25 to 2.0 mg daily qd**

After six months, give patient a *Hormonal Holiday:*

1. **Take all of the hormones Monday-Saturday; none on Sunday.**

OR

1. **Take all hormones days 1–25 of month; with 4 or 5 days off.**

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Estradiol-Specific

Salivary Lab Value	Bi-est Cream	E3/E2 Ratio
2.8-3.8 pmol/L	0.75-1.00 mg	50%/50%
3.8-4.8 pmol/L	0.25-0.5 mg	50%/50%
4.8-6.0 pmol/L	0.25-0.75 mg	80%/20%
6.0-8.2 pmol	0.25-0.75 mg	90%/10% mg
>8.2 pmol	None	None

Female Hormone Protocol

By Pamela W. Smith, MD, MPH, MS

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Progesterone

Progesterone Apply @ Bedtime Nites 14-25

Salivary Lab Value	Progesterone Cream	Progesterone E4M Cap
328-450 pmol/L	25-30 mg	200-250 mg
450-700 pmol/L	20-25 mg	140-200 mg
700-900 pmol/L	15-20 mg	120-150 mg
900-1000 pmol	5-10 mg	90-120 mg
1000-1385 pmol	None	None

Herbal Remedy -Chasteberry or Swedish Pollen Extract

Female Hormone Protocol

By Pamela W. Smith, MD, MPH, MS

fppt.com

Testosterone

- **Normal: 34–148 pmol/L**
- **Goal is around 70–100 pmol/L**

Saliva Lab Test	Testosterone Cream
<30 pmol/L	1-2 mg
30-40 pmol/L	0.75 mg-1 mg
40-60 pmol/L	0.5-0.75 mg
60-75 pmol	0.25-0.5 mg
>75	No Testo

Female Hormone Protocol

By Pamela W. Smith, MD, MPH, MS

- ***Change Site Daily*** **(Will grow black hairs if site repeated)**
- ***Apply to thigh or buttocks*****-Rub in for 1-2 minutes**
- ***Can Transfer*** ***for up to 2 hours*****-Gentlemen callers, Lady friends, Children, Goldfish, Golden Retrievers, The Gardner**

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BHRT Pellets

- Long acting, 3-5 months for women and 4-6 months for men
- FDA approved 75-mg testosterone pellet in 1972.
- Avoids fluctuations in hormone levels
- Shortest onset of action of all HRT (4-7 days)
- No increase the risk of blood clots
- Superior in relieving menopause symptoms
- Maintains bone density, restoring sleep patterns
- Improved sex drive, libido, sexual energy, response, performance.
- Rx:
  - Migraine, menstrual headaches, vaginal dryness, urinary incontinence, urgency and frequency

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To Complete the Picture

Hormones

- ***Pregnenolone***
  - **Memory, Neuroprotective**
- ***DHEA***
  - **Regenerates myelin, antidepressant, regulates mood, ⇩ inflammatory cytokines and interleukins**
- ***Cortisol***
  - **Stress, ⇧ rT3**
- ***Melatonin***
  - **Antioxidant, Resets Daily Rhythm, Antineoplastic**
- ***Prolactin***
  - **High-Pituitary Tumor *(Adenoma)***
  - **Low-Treatment Resistant *Anxiety***

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Clinical Perles

Estrogen

- Progesterone Offset
- Weight Loss
- Liver Detox
- U.S. Pelvis Re: FIbroids, Tumor
- If Estrone 7 keto DHEA (25-50 mg.)

Progesterone

- Chasteberry
- Swedish Pollen Extract

Testosterone

- Saw Palmetto 240-260 mg 1-2 x/d
- Metformin 500 mg/d + CoEnzyme Q10 100 mg +B Complex 100 1-2/d
- Spironolactone 100 mg BID If DHEA is too high, this can be due to stress,

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Clinical Perles

Vaginal Dryness

Estriol vaginal cream 0.5 mg to 2 mg.

RX: Estriol Vaginal Cream (or suppository) 1 mg in 50% VersaBase® and 50% MucoLox™

Sig: Insert vaginally nightly for two weeks, then

Monday, Wednesday, Friday X 2 weeks, then PRN.

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Fixing Marie

2/26/17

2/26/17	*Marie*	*Median*
Testosterone Free	1.3 pg/ml	2-4 pg/ml*
Testosterone Total	19.0 ng/ml	<44 ng/ml*
DHEA-S	77 ug/dl	195 ug/dl*
Estrone (E1)	42 pg/ml	< 200 pg/ml*
Estradiol (E2)	<0.5 pg/ml	90 pg/ml*
Progesterone	0.12 ng/ml	5-7 ng/ml*
Pregnenolone	108 ng/dl	100 ng/dl*
EP Ratio	420	< 250

25 OH D 41 (50-80)

Homocysteine 14.2 (<10)

Hct 37.5

cRP 2.07 (<1.0)

5/1/2017

5/1/17	*Marie*	*Median*
Testosterone Free	2.8 pg/ml	2-4 pg/ml*
Testosterone Total	32.1 ng/ml	<44 ng/ml*
DHEA-S	152 ug/dl	195 ug/dl*
Estrone (E1)	78 pg/ml	< 200 pg/ml*
Estradiol (E2)	<0.5 pg/ml	90 pg/ml*
Progesterone	2.1 ng/ml	5-7 ng/ml*
Pregnenolone	103 ng/dl	100 ng/dl*
EP Ratio	38	< 250

25 OH D 58

Homocysteine 12.5

Hct 39.5

cRP 1.47

Fixing Marie

Sleep ***(2 hours before bedtime)***

Vitamin D3 2000 IU 2 hours bedtime- (25 OH D 41)

Magnesium TAurate 100 mg 1-2 2 hours before bedtime

Melatonin 0.5 mg 1 2 before bedtime

CV, Nutritional Marker**-Homocysteine 14.2**

Rx. Methylated B6, B12, Folic Acid, TMG, Betaine 1 in am, 1 in pm

Thyroid Antibodies **TPO, TAG**

Rx. Plant Sterolins 1 in am, 1 in Pm

Inflammation

cRP 2.07 (normal, not optimal)

Rx Omega-3 Fatty Acids (Fish Oil) 1000 MG Oral Capsule BID

Curcumin 500 mg 1-2 in am , 1-2 in pm

GI**-Digestive Enzymes**

Probiotic, L-Glutamine

Fixing Marie

Plan: **AIP Diet, Aerobic, Anaerobic Exercise 5x/wk 45 min/session**

Hormones: ***Bi-est 2.2 mg/Progesterone 100 mg/Testosterone 1mg/gm***

1 gm daily to inner thigh or inner arm

E/T Precursors **(DHEA-s 77 + Memory loss)**

DHEA 10 mg 1/ day + 25 mg Pregnenolone

Insulin Resistance **(IR = 3.75)**

Ceylon Cinnamon, 1 tsp/d

Berberine 1/d

Urinary Incontinence- **(Pt. Stopped after 2 weeks on Testosterone)**

Cranberry 1/d

Berberis vulgaris (10 drops in 4 oz. water 2x/d)

Thyroid

Levothyroxine Sodium 125 MCG 1 in am on an empty stomach

Liothyronine 5 MCG 1 in am, 1 @ noon empty stomach

Estrogen in Men

Estrogen levels increase as men age due to:

- **Increases in aromatase activity**
- **Obesity**
- **Alcohol excess**
- **Environmental estrogens**
- **Estrogen containing food**
- **Zinc deficiency**
- **Liver dysfunction**
- **Supraphysiologic Testosterone Therapy**
- **Calcium deficiency**
- **Diabetes**

Optimal Levels 20-30 pg/ml

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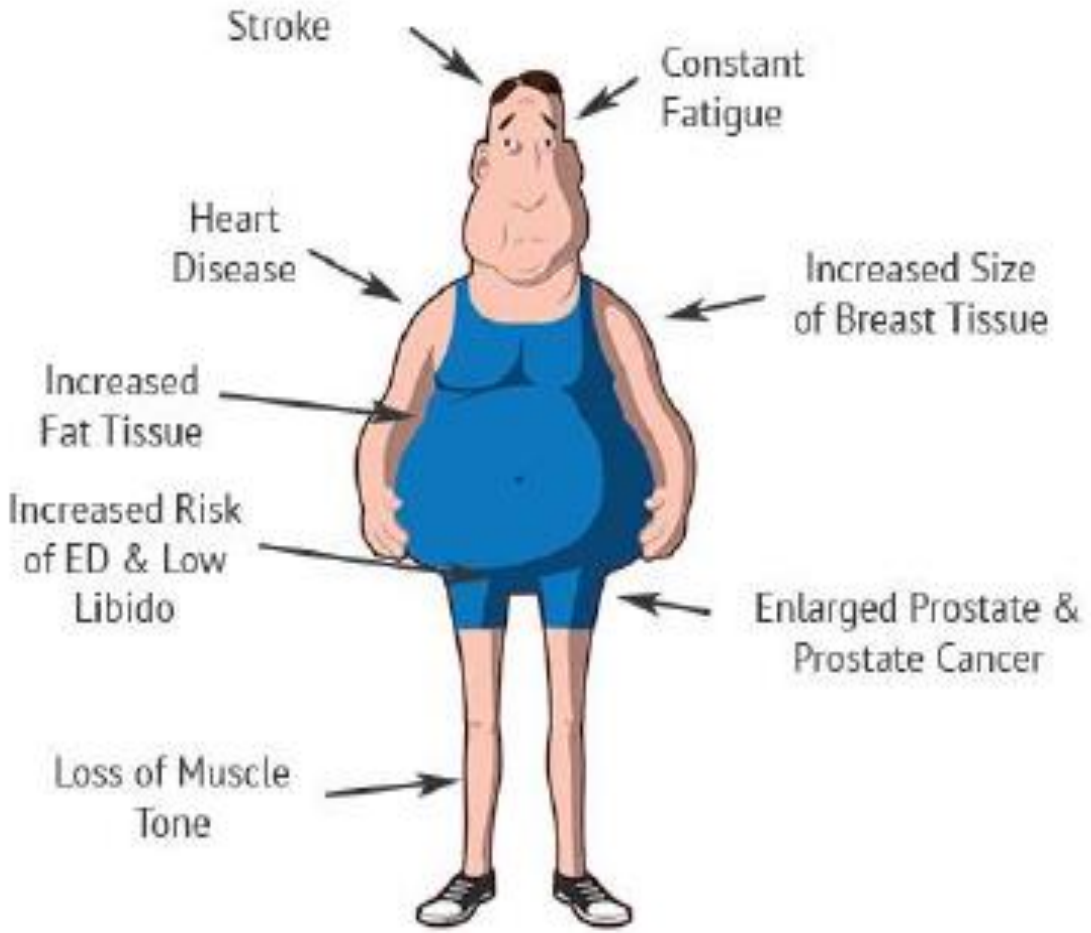
High Estrogen in Men



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Estrogen at Physiologic Levels in Men

Cardioprotective

- Men with higher estradiol levels had twice the risk of Sudden Cardiac Death
- High estradiol levels in men were associated with acute myocardial infarctions.
- High estradiol in males associated with an increased risk of stroke.
- High estradiol in males is associated with increased PVD

- Mohamad, M., "Serum levels of sex hormones in men with acute myocardial infarction," Neuro Endocrinol Lett 2007; 28(2):182-86.
- Abbott, R., et al., "Serum estradiol and risk of stroke in elderly men," Neurology 2007; 68(8):563-68.
- Tivesten, A., et al., "Low serum testosterone and high serum estradiol associated with lower extremity peripheral arterial disease in elderly men. The MrOS Study in Sweden," Jour Amer Coll Cardiol 2007; 50(11):1070-76

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Estrogen in Men

Symptoms of Estrogen Elevation Include:

1. **Sexual Dysfunction**
2. **Gynecomastia**
3. **Symptomatic BPH**
4. **Increased Abdominal Fat**
5. **Fatigue**
6. **Loss of Muscle Mass**
7. **Emotional Outbursts, Depression**
8. **Diabetes Type 2**

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Estrogen in Men

- **Male: Daily Testosterone production rates range from *4 to 11.8 mg per day.***
  - **Ave = 28 mg - 80 mg/week.**
- **Female: Daily Testosterone production rates ranged from *.9 mg to 2.8 mg per day*.**
  - **Ave=6.3mg to 20mg/week.**

Testosterone Production Rates In Normal Adults. Journal of Clinical Investigation Vol. 42, No. 11, ***1963***, Stanley G. Korenman, Hildegard Wilson, Mortimer Lipsett, Endocrinology Branch, National Cancer Institute, Bethesda, MD.

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Supraphysiologic Testosterone Doses

↑ **Estrogen/DHT**

↓ **Central Neurosteroids**

↓ **(Allopregnenolone,Pregnenolone, Deoxycorticosterone)**

↑ **GABA (inhibitory neurotransmitter- i.e. (-) x (-) = (+)**

IL-1, IL-2, IL-6, TNF-a, and IFN-gamma ↑ E-2

=

Agitation, Aggression, Irritability

– **EBlocker+Loss of E Brain Production, ↓ Blood Flow,**

• **↓ E Stimulation of HGH**

Testosterone Production Rates In Normal Adults. Journal of Clinical Investigation Vol. 42, No. 11, ***1963***, Stanley G. Korenman, Hildegard Wilson, Mortimer Lipsett, Endocrinology Branch, National Cancer Institute, Bethesda, MD.

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Avoid Estrogen Excess and Use of E Blocker by Avoiding Supraphysiologic Doses of Testosterone

- RX
  - Zinc Citrate (30-90 mg/d)
  - Quercetin
  - Glycyrrhiza – licorice
  - Grape seed extracts composed mainly of proanthocyanidins
  - Resveratrol
  - DIM (1-3 gm/d p.o.}
  - Chrysin (250 mg bid p.o., topical 50 mg/d)
  - Progesterone Cream 2-5%, Caps 10-15 mg/d
  - Myomin
  - Berberine
  - Vitamin K
  - Anastrozole (0.5-1.0 mg 1-3x/wk)

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Zinc Citrate

- Deficiency associated with decreased Testosterone, increased Estradiol.
- Synthesizes and secretes LH and FSH
- Essential role in gonadal differentiation, testicular growth and development of seminiferous tubules, spermatogenesis, testicular steroidogenesis, androgen metabolism and interaction with steroid receptors.
- Zinc supplementation results in an increase in serum testosterone.
- Acts as Aromatase (Estradiol Synthetase Enzyme).

Dose: Zinc Citrate

» Zinc less than 50 mcg/dL; RX 30mg Zinc Citrate BID to TID
» Zinc greater than 50 mcg/dL; 30 mg/Day

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Diindolylmethane (DIM)

Diindolylmethane (DIM)

A metabolite of indole–3–carbinol (I3C) found in:

Cruciferous vegetables such as; Broccoli, Kale and Brussels sprouts.

Anti-carcinogenic, anti-oxidant, anti atherogenic effects

Inhibits Microglial Hyperactivation and Attenuates Brain Inflammation

Reduces TNF-alpha, IL-6, IL-Beta, NF-*KB, PGE2*

Dose: 100 mg 2-3 x/d

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Estrogen Self Assessment

S/S Estrogen Deficiency	S/S Estrogen Excess
Poor /Non existent libido	Fluid Retention
Drooping Breasts	Cervical Dysplasia/Fibroids
Vaginal Dryness	Hypothyroidism
Urinary incontinence/Infections	Fatigue
Hot Flashes	Insomnia/Poor Sleep
Night Sweats	Bloating
Brain Fog	Anxiety/Fear
Memory Issues	Breast Swelling/Tenderness
Irregular Menstrual Cycles	Severe Headaches
Amenorrhea	Excess Menstrual Bleeding
Thinning Skin	Weight Gain
Wrinkles Especially Around Mouth	Increased Breast Cancer Incidence In Men
Increased Insulin Resistance	Breast Enlargement
Osteoporosis	Prostate Enlargement
Diabetes	Difficulty Urinating
Elevated Lipids	Increased Emotional Lability
Heart Disease	Tearfulness

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Estrogen Quiz[23]

	Never				Always
1. I am losing hair on top of my head.	0	1	2	3	4
2. I have hot flashes	0	1	2	3	4
3. I have night sweats	0	1	2	3	4
4. My breasts are droopy	0	1	2	3	4
5. I feel tired constantly	0	1	2	3	4
6 I am depressed	0	1	2	3	4
7. I have vaginal dryness	0	1	2	3	4
8. My thinking is foggyq	0	1	2	3	4
9. I have wrinkles around my lips	0	1	2	3	4
10. I have less interest in sex	0	1	2	3	4

Add up your Overall Score _____: 10 or less: Satisfactory level. Between 11 and 20 : Possible Estrogen Deficiency. 21 or greater Probable Estrogen deficiency

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