Reproductive Hormonal Issues: Treating Mood Disorders Associated with PMS and Peri-menopause

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Dr. Anna Cabeca

- Emory University trained, Board Certified Gynecologist and Obstetrician
- Board Certified in Anti-Aging & Regenerative Medicine
- Expert, Functional Medicine & Women's Health, Hormone therapy
- Lecturer, Consultant, and Trainer

Objectives

- Identify important clues in the patient history and physical exam that identify mood disorders in PMS, postpartum, and the perimenopausal transition (PMT).
- Evaluate the role of diet, specific nutritional supplements, and hormonal and botanical therapies in improving mood disorders in women with PMS, premenstrual dysphoric disorder (PMDD), postpartum depression, and during the PMT.
- Promote hormonal balance through integrative medicine, detoxification, nutrition, alkalinization, and digestive health.
- Empower our bodies, spirits, and minds to create balance and health.

My Story - BEFORE

- 40 year old with 4 children
- Worked over 80 hrs/week
- Primary bread winner
- Losing hair
- 80 lbs overweigh
- Menopausal and
- Depressed

The soul suffers when the body is diseased or traumatized, while the body suffers when the soul is ailing - Aristotle

My Story - AFTER

- Hair grew back
- Lost over 80 lbs
- Fertile again… meet my miracle - Ava!
- Wake up excited each morning

Head-to-Toe Approach

- Mind, Spirit, Energetics
- Environment
- Nutrition
- Digestion and Intestinal Health
- Detoxification
- Hormone Health and Balance
  - HPTAG Axis
  - Neuro-endocrine Health
- Structure and Function
  - Exercise & Mobility

"75% of an individual's health after age 40 is dependent upon what the person has done to his or her genes, not the genes themselves."

25%

75%

Jeffrey S. Bland, Ph.D.
Genetic Nutritioneering, 1999, p. 65

Linus Pauling's Orthomolecular (right molecules) Medicine

1. **Everyone is different.**
2. **Each individual's health benefits from having the right molecules in the right amounts.**
3. ***Before turning to medicines, we should attempt to adjust the normal body constituents to match the needs for optimal functioning.***

Individualized Care

- Physically
- Physiologically
- Biochemically
- Spiritually

Individualized evaluation
⇒⇒ Individualized treatment

Inflammation & Hormone Imbalance

Precursor to disease states

- Diabetes mellitus
- Arthritis
- Alzheimer's disease, Cognitive decline
- Cardiovascular disease
- Stroke
- Cancer
- Endometriosis, Fibroids, Infertility
- PMS
- Depression
- Obesity

Factors Creating Hormone Imbalance

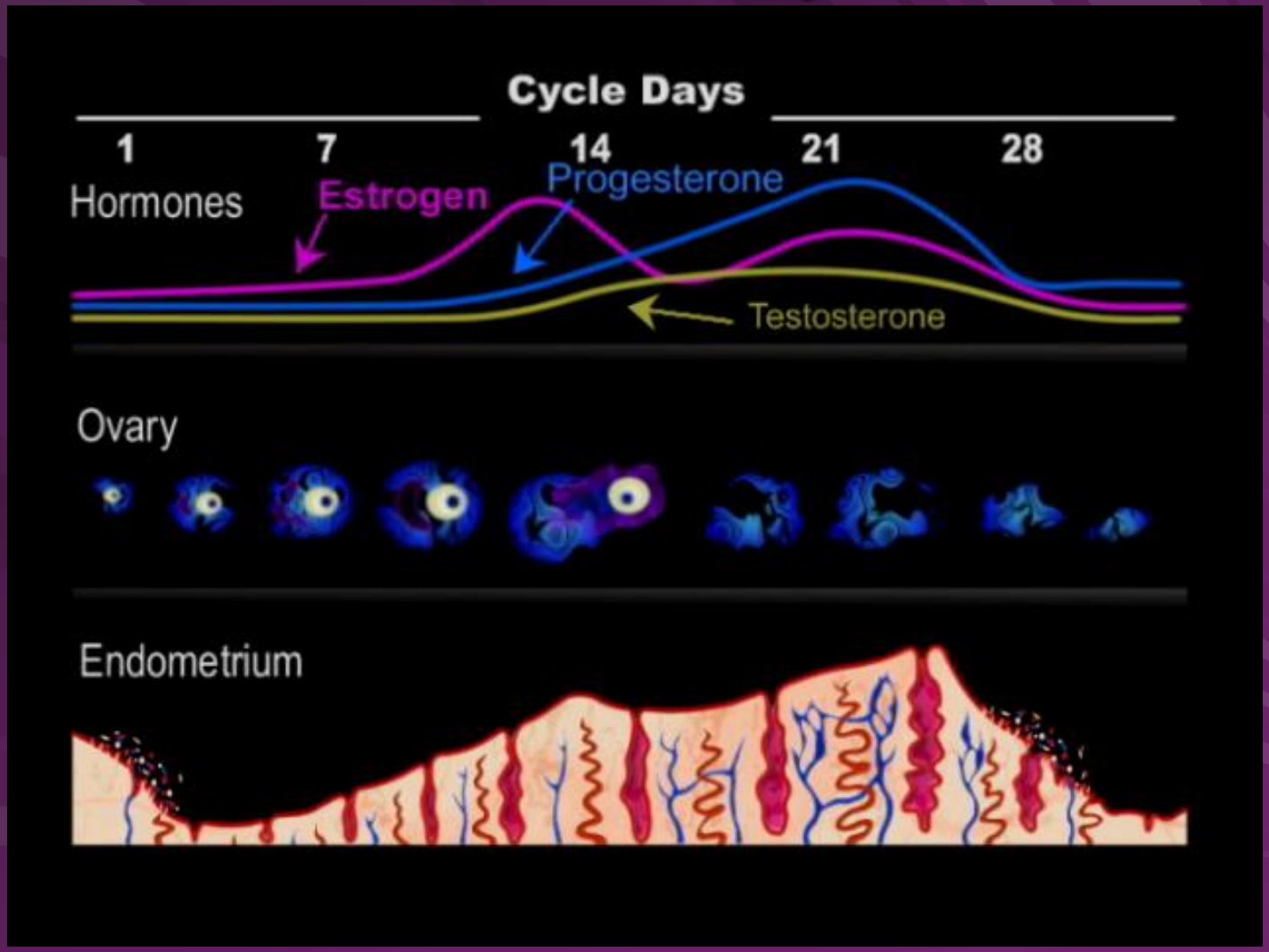
- Stress
- Dietary Habits
- Certain nutrient deficiencie
- Dysbiosis
- Hormonal disruptors
- Toxins
- Other health problems suc adrenal, ↑ or ↓BMI
- Natural aging
- Insomnia
- Genetics

Inflammation & Hormone Imbalance

- At time of menopause a woman's average life expectancy is 32.7 years
- 1:2 Osteoporotic Fracture
- 1:3 Coronary Heart Disease
- 1:5 Stroke or Alzheimer's
- 1:8 Breast Cancer

Kung HC, Hoyert DL, Xu J, Murphy SL. Deaths: final data for 2005. Natl Vital Stat Rep 2008;56:1-120

Menstrual Cycle



Premenstrual Syndrome (PMS)

- **Definition of PMS:**
  - **The cyclic appearance of one or more of a large constellation of symptoms (200)**
  - **Lifestyle or work is affected**
  - **Followed by a period of time entirely free of symptoms.**
  - **The most frequently encountered symptoms include the following: abdominal bloating, anxiety, breast tenderness, crying spells, depression, fatigue, irritability, thirst and appetite changes, and variable degrees of edema of the extremities**
  - **Occurring within the last 7 – 10 days of the cycle**
    - **Speroff L. Clinical Gynecologic Endocrinology and Infertility 7th ed 2005 pg 531-533.**

- According to the US Bureau of the Census, women aged 45-64 years, who are in their late and post reproductive years, constitute over 26% of the female population

Zoe R. 36 y.o.

- Cc: PMS, moodiness, breast tenderness, having difficulty organizing tasks, memory loss, decreased libido
- PM/Shx: neg, G4P4004;
- WDWN, 5'11", 155 lbs., fcb b/l, areolar and vaginal mucosal palor

Hormone Test	Result		L	WR	H	Expected Range
Estriol		pg/ml				(1) <30.0 females non-pregnant
Estradiol	2.3	pg/ml		X		(1) 1.0-3.2 post; (2) 1.0-10.8 pre; (3) 1.5-10.8 supplementation; (4) <2.5 males
Progesterone	45.0	pg/ml	X			(1) 18-126 post; (2) 127-446 pre (luteal); (3) 500-3000 supplementation; (4) <51 males
Ratio of Pg/E2	19.2		X			(1) 200-600 females; (2) 200-300 males;
Testosterone	35.6	pg/ml		X		(1) 30.1-142.5 males; (2) 6.0-49 females; (3) 30-60 therapy females; (4) 250-350 therapy males;
DHEA	95.0	pg/ml	X			(1) 137-336 males; (2) 106-300 females
Cortisol Morning	7.3	nmol/L		X		(1) 5.1-40.2
Cortisol Noon		nmol/L				(1) 2.1-15.7
Cortisol Evening		nmol/L				(1) 1.8-12.1
Cortisol Night	0.8	nmol/L	X			(1) 0.9-9.2

*DHEA and Testosterone results are for investigational use only

L=Low(below expected range) WR=Within Range(within expected range) H=High(above expected range)

Zoe R. 36 y.o

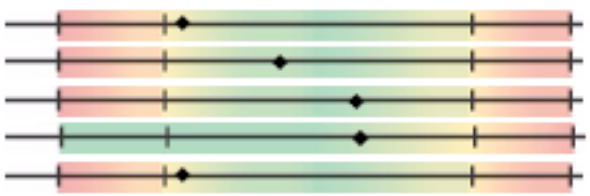
4146 Women's Health Profile

Methodology: Immunometric Assay, Enzymatic Assay,GC/MS, LC/Tandem Mass Spectrometry, ICPMS,HPLC-TBARS, Colorimetric

Endocrine

Insulin Sensitivity

		Results	Low Limit	High Limit	Reference Limits	
1	Insulin	3.0			2.0 - 12.0	uIU/mL
2	Glucose	84			70 - 105	mg/dL
3	HDL Cholesterol	69			30 - 85	mg/dL
4	LDL Cholesterol (Direct)	74			<= 130	mg/dL
5	Triglycerides	42			35 - 160	mg/dL



Estrogen Metabolism

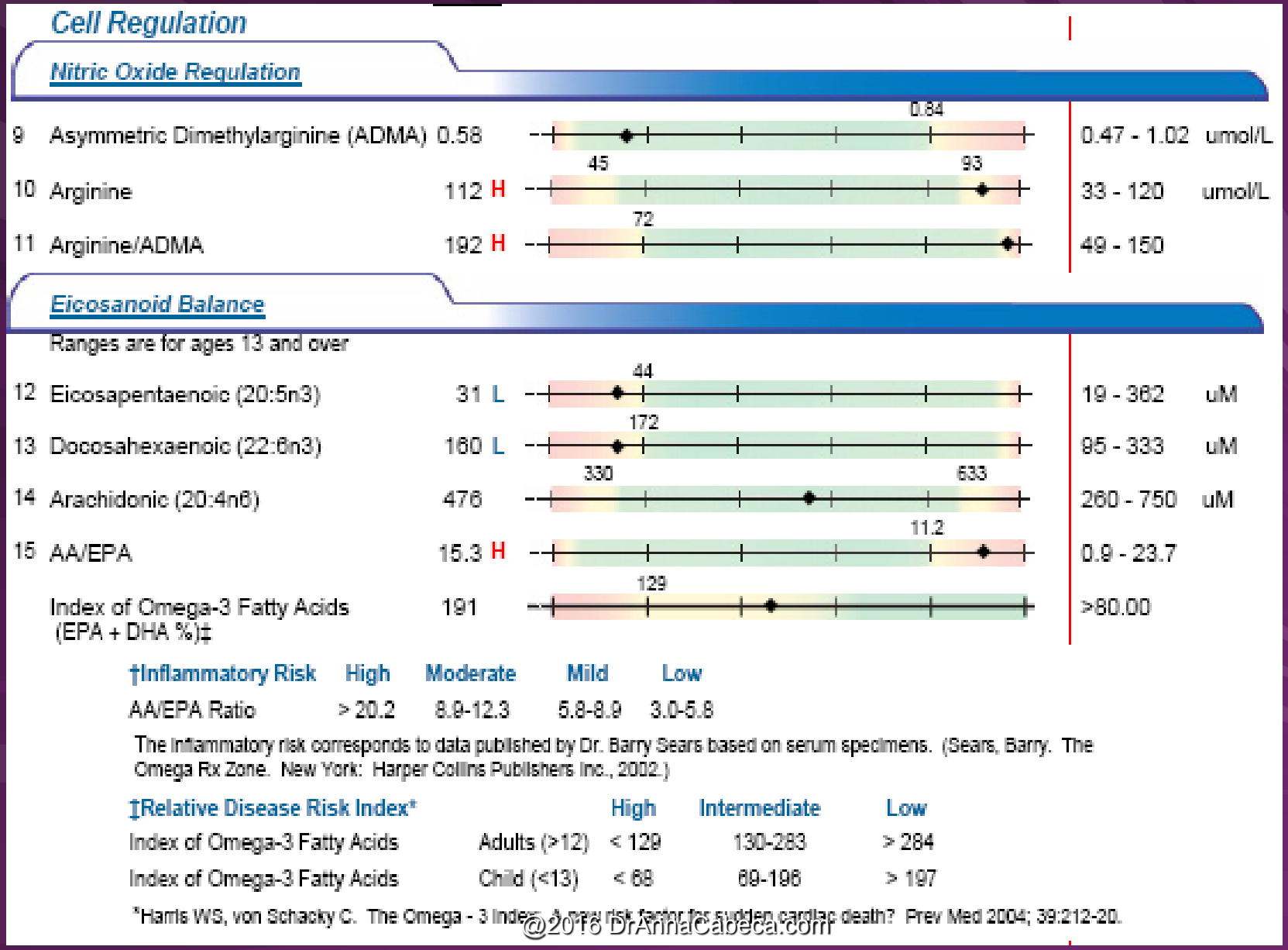
		Results	Normal Limits			
		ng/mg crea	Pre-Menopausal	Post-Menopausal without estrogen therapy	Post-Menopausal with estrogen therapy	
6	2-Hydroxyestrogens (2OHE)	16.4	3 - 40	2 - 10	10 - 75	
7	16-Hydroxyestrone (16OHE1)	10.1	3 - 30	2 - 8	5 - 25	
8	2:16 Ratio	1.62 L				2.00 - 8.00

Creatinine =218 mg/dL

The ideal value for the 2/16 ratio is above 2.0. The following have been shown to raise the ratio:

- Cruciferous vegetables (e.g., broccoli, brussel sprouts, cabbage, cauliflower).
- Supplementation of indole-3-carbinol (I-3-C) or diindolylmethane (DIM)
- Soy isoflavones
- Flax seeds (not oil)
- Omega-3-fatty acids (DHA & EPA) found in fish (e.g. mackerel, lake trout, herring, sardines, salmon) and marine algae also may help to lower cancer risk. Assure antioxidant adequacy when adding polyunsaturated oils.

Z.R. 36 y.o



Cell Regulation

Nitric Oxide Regulation

9	Asymmetric Dimethylarginine (ADMA)	0.58		0.47 - 1.02	umol/L
10	Arginine	112 H		33 - 120	umol/L
11	Arginine/ADMA	192 H		49 - 150	

0.84
45
93
72

Eicosanoid Balance

Ranges are for ages 13 and over

12	Eicosapentaenoic (20:5n3)	31 L		19 - 362	uM
13	Docosahexaenoic (22:6n3)	160 L		85 - 333	uM
14	Arachidonic (20:4n6)	476		260 - 750	uM
15	AA/EPA	15.3 H		0.9 - 23.7	
	Index of Omega-3 Fatty Acids (EPA + DHA %)‡	191		>80.00	

44
172
330
633
11.2
129

†Inflammatory Risk	High	Moderate	Mild	Low
AA/EPA Ratio	> 20.2	8.9-12.3	5.8-8.9	3.0-5.8

The inflammatory risk corresponds to data published by Dr. Barry Sears based on serum specimens. (Sears, Barry. The Omega Rx Zone. New York: Harper Collins Publishers Inc., 2002.)

‡Relative Disease Risk Index*		High	Intermediate	Low
Index of Omega-3 Fatty Acids	Adults (>12)	< 129	130-283	> 284
Index of Omega-3 Fatty Acids	Child (<13)	< 68	69-196	> 197

*Harris WS, von Schacky C. The Omega - 3 Index: A new risk factor for sudden cardiac death? Prev Med 2004; 39:212-20.

Z.R. 36 y.o.

Cell Protection

Cell Membrane Oxidation

16	Lipid Peroxides	0.6		<= 2.0	nmol/mL

Elemental Cofactor Status

Results are expressed as ppm packed cells.

17	Magnesium	24 L		18 - 40
18	Zinc	5.3 L		4.2 - 9.3

Georgia Lab Lic. Code #067-007
CLIA ID# 11D0255349

New York Clinical Lab PFI #4578
Florida Clinical Lab Lic. #800008124

Laboratory Directors
J. Alexander Bralley, PhD

Metabolic Markers

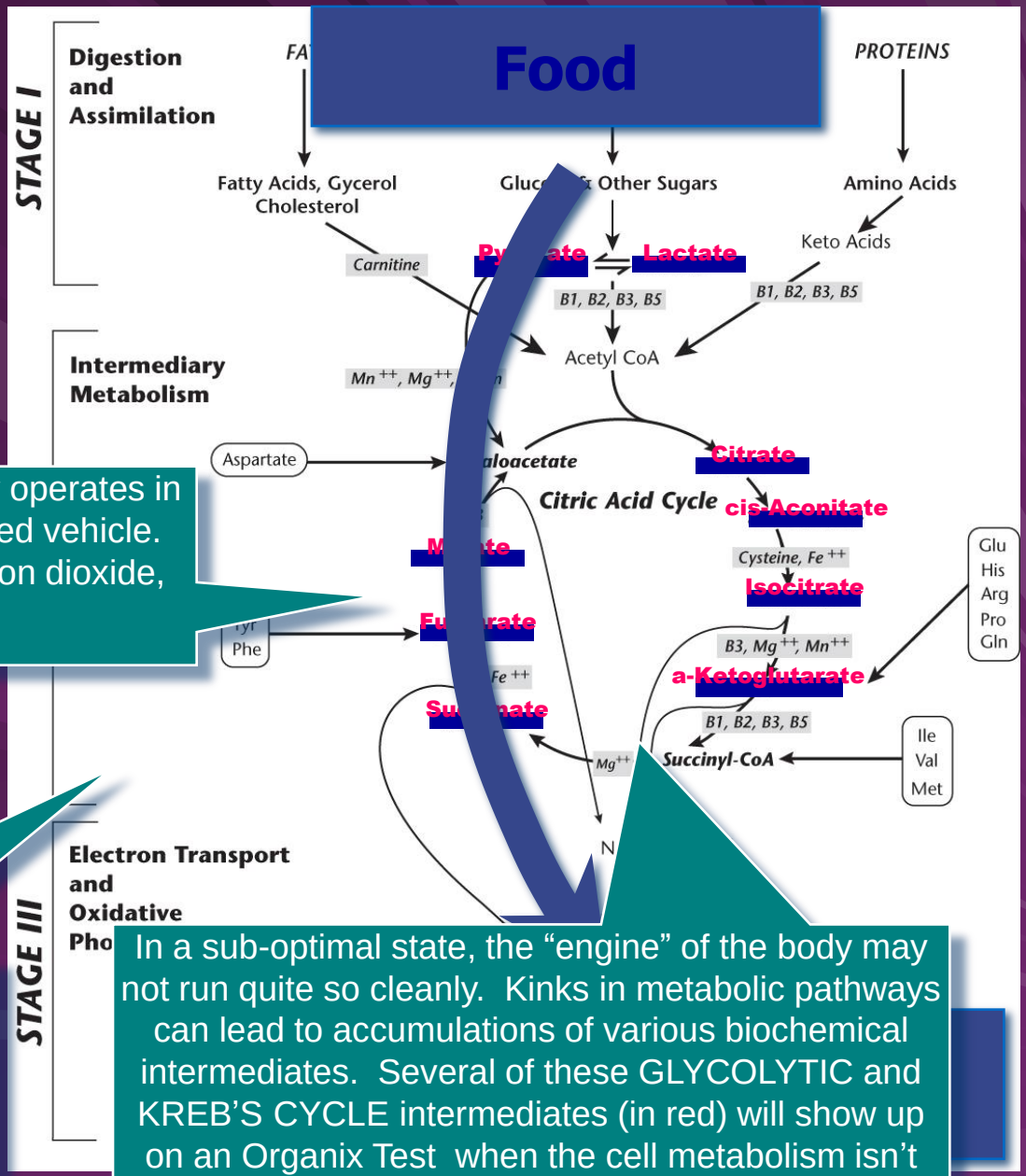
B-Vitamin Insufficiency

19	Pyruvate	3.3		<= 7.1
20	a-Ketoglutarate	19.5		2.6 - 60.0
21	a-Ketoisovalerate	0.24		<= 0.94
22	a-Ketoisocaproate	0.22		<= 0.58
23	a-Keto-ß-Methylvalerate	0.7		<= 2.7
24	Xanthurenate	0.4		<= 1.2
25	ß-Hydroxyisovalerate	3.0		<= 15.3
26	Methylmalonate	2.1		<= 3.4
27	Formiminoglutamate	0.58		<= 2.28

Cellular Energy

28	Adipate	7.2 H		<= 10.3
29	Suberate	1.6		<= 3.3
30	Ethylmalonate	4.7		<= 8.5
31	ß-Hydroxybutyrate	0.5		<= 12.8
32	Succinate	2.8		1.1 - 34.0
33	Fumarate	0.45		<= 1.40

Stages of Energy Extraction From Food



In a very healthy state, the body operates in a similar fashion to a finely tuned vehicle. Pure air and food in: Pure carbon dioxide, water, and urea out.

The following flowchart is not unlike the cellular "engine" of the body. Food macronutrients serve as the raw fuel – transitioned into carbohydrate, fat, and protein energy resources that the cell uses to build ATP.

In a sub-optimal state, the "engine" of the body may not run quite so cleanly. Kinks in metabolic pathways can lead to accumulations of various biochemical intermediates. Several of these GLYCOLYTIC and KREB'S CYCLE intermediates (in red) will show up on an Organix Test when the cell metabolism isn't running smoothly.

Z.R. 36 y.o. 2/2008

Neural Function

36	Vanilmandelate	4.0	H	1.1 – 3.8	0.4 - 5.3
37	Homovanillate	3.9		1.6 – 7.7	0.7 - 17.0
38	5-Hydroxyindoleacetate	2.5		1.5 – 6.3	0.7 - 26.0
39	Kynurenate	1.7	H	1.6	<= 2.5
40	Quinolinate	5.0		10.2	<= 16.5

Detoxification

41	Citrate	460		948	127 - 1,550
42	Cis-Aconitate	38		76	29 - 122
43	Isocitrate	70		92	36 - 130
44	2-Methylhippurate	0.010		0.047	<= 0.106
45	Orotate	0.4		1.0	<= 1.6
46	Glucarate	3.8		7.0	<= 11.9
47	a-Hydroxybutyrate	0.3		1.2	<= 2.2
48	Pyroglutamate	45	H	43	< 72

Creatinine =218 mg/dL

Zoe R.

- Therapeutic life style changes
- Dietary recommendations/detox program
- Progesterone cream 60 mg/ml ½ ml on cycle day 10 -28
- DHEA 15 mg/d
- Daily vitamin packs (multivitamin with minerals, MCHC calcium, Omega 3 360/240 mg EPA/DHA), Carnitine 500mg, Magnesium Glycinate, Zinc 50 mg, Glycine, NAC, Vitamin C 1000 mg, Vit E (mixed tocotrienols) 400IU, Iodide 25mg per day

The Perimenopausal Transition (PMT)

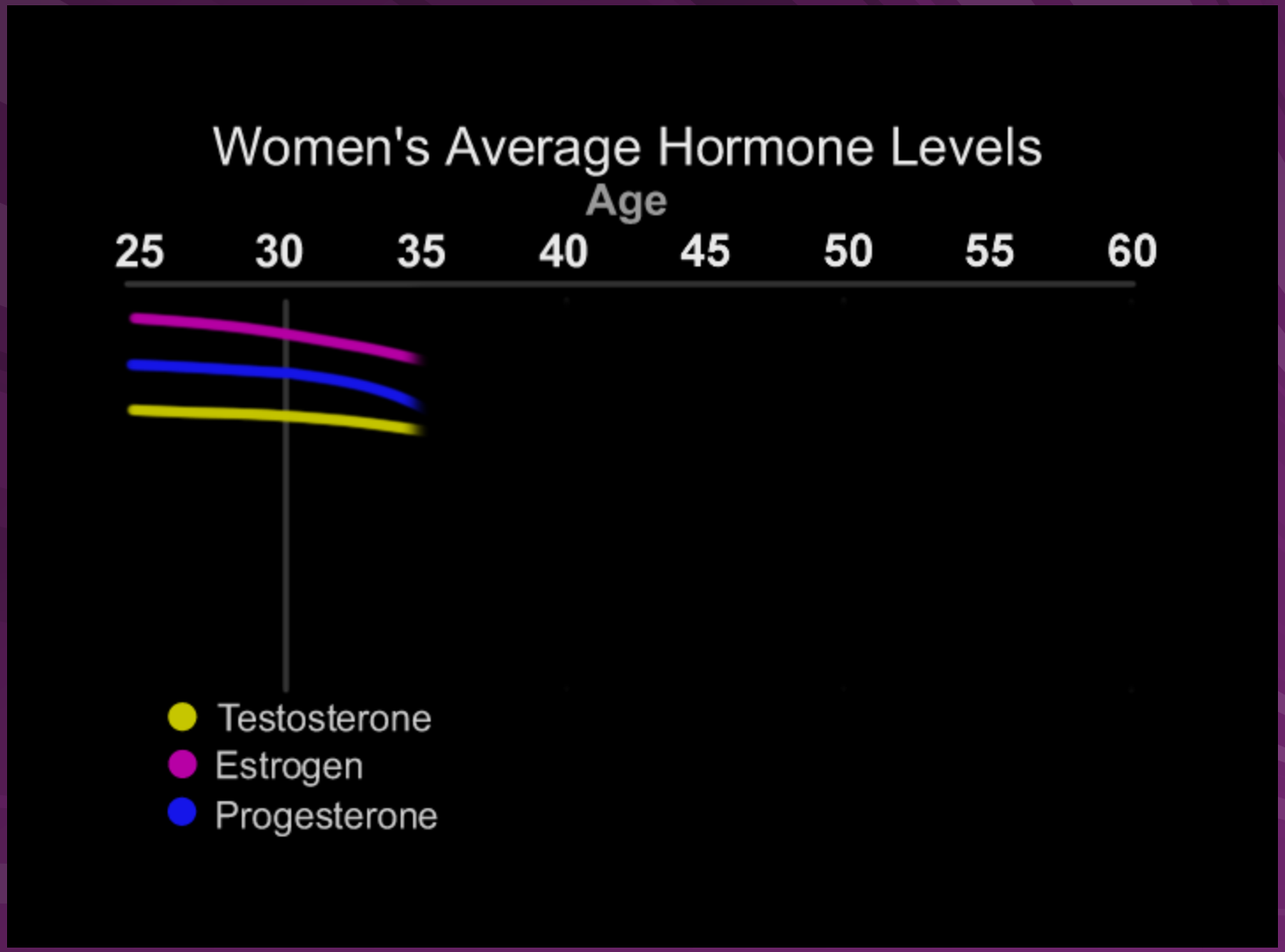
- Average age of onset = 46 y
- Age of onset for 95% of women = 39 - 51 y
- Average duration = 5 y
- Duration for 95% of women = 2 – 8 y
- < 10% abruptly cease menses
- When FSH >20 IU/L, and LH >30 IU/L, pregnancy unlikely
  - Speroff L Clinical Gyneocologic Endocrinology and Infertility 7th ed 2005

Symptoms of Estrogen Dominance

- Mood Swings
- Irritability
- Depression
- Irregular Periods
- Heavy Menstrual Bleeding
- Hot Flashes
- Vaginal Dryness
- Water Retention
- Weight Gain: Hips, Thighs and Abdomen
- Sleep Disturbance (Insomnia, less REM sleep)

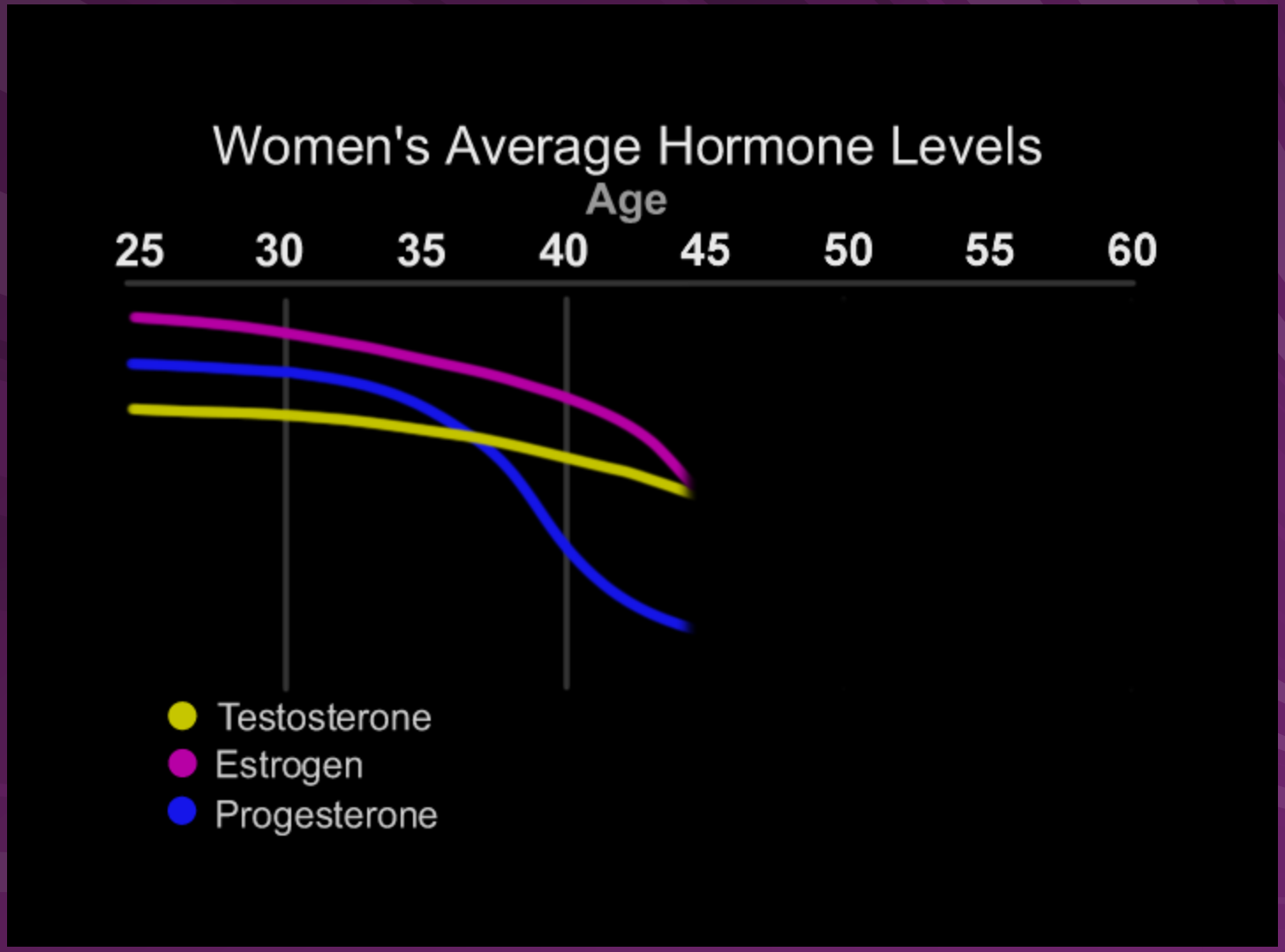
- Decreased Libido
- Headaches
- Fatigue
- Short-term Memory Loss
- Lack of Concentration
- Thinning of Scalp Hair
- Dry, Thin, Wrinkly Skin
- Increased Facial Hair
- Bone Mineral Loss (Osteoporosis) (Athletes Δ)
- Diffuse Aches and Pain

Women’s Average Hormone Levels



The Complete HORMONE makeover

Women’s Average Hormone Levels



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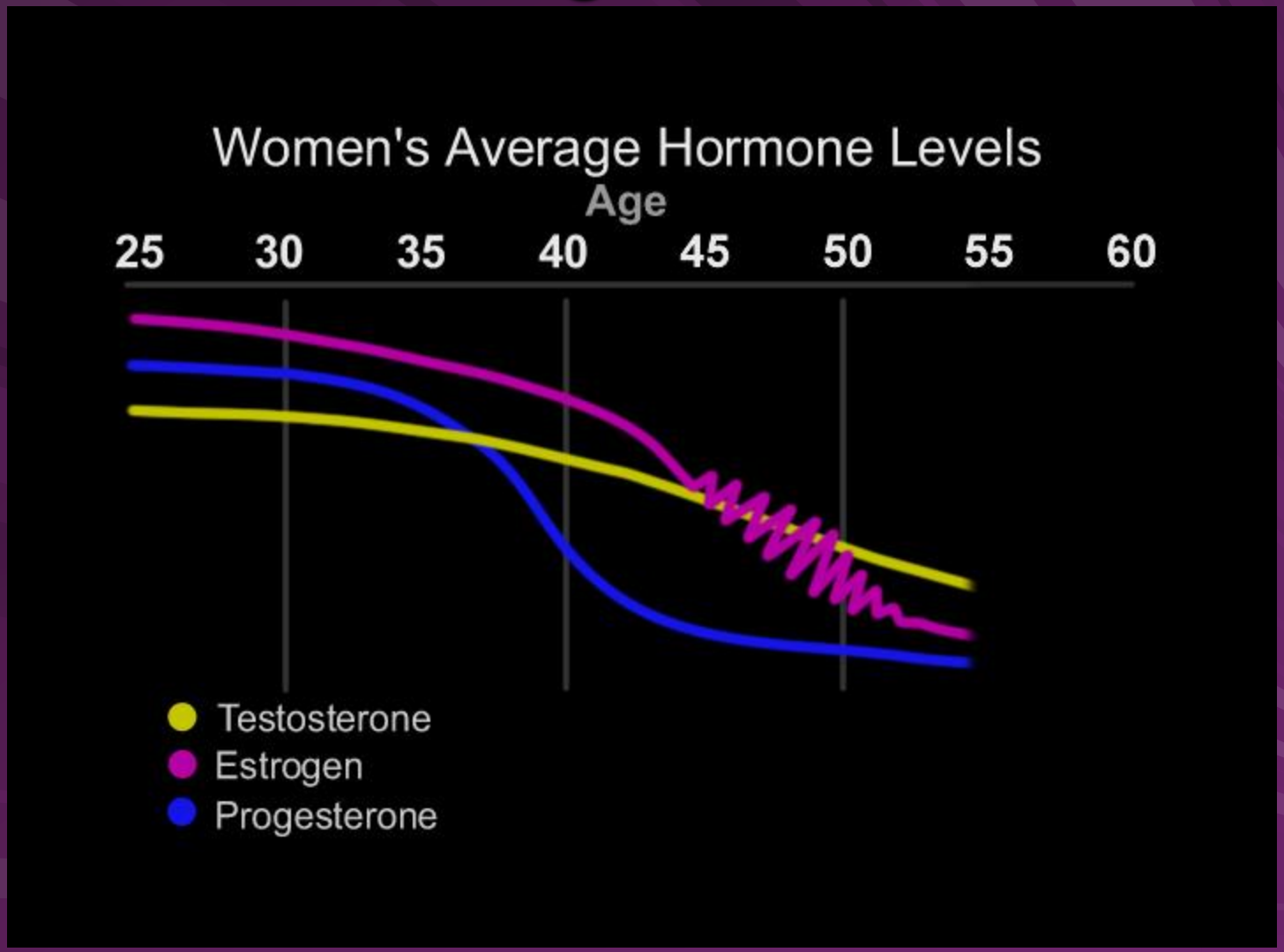
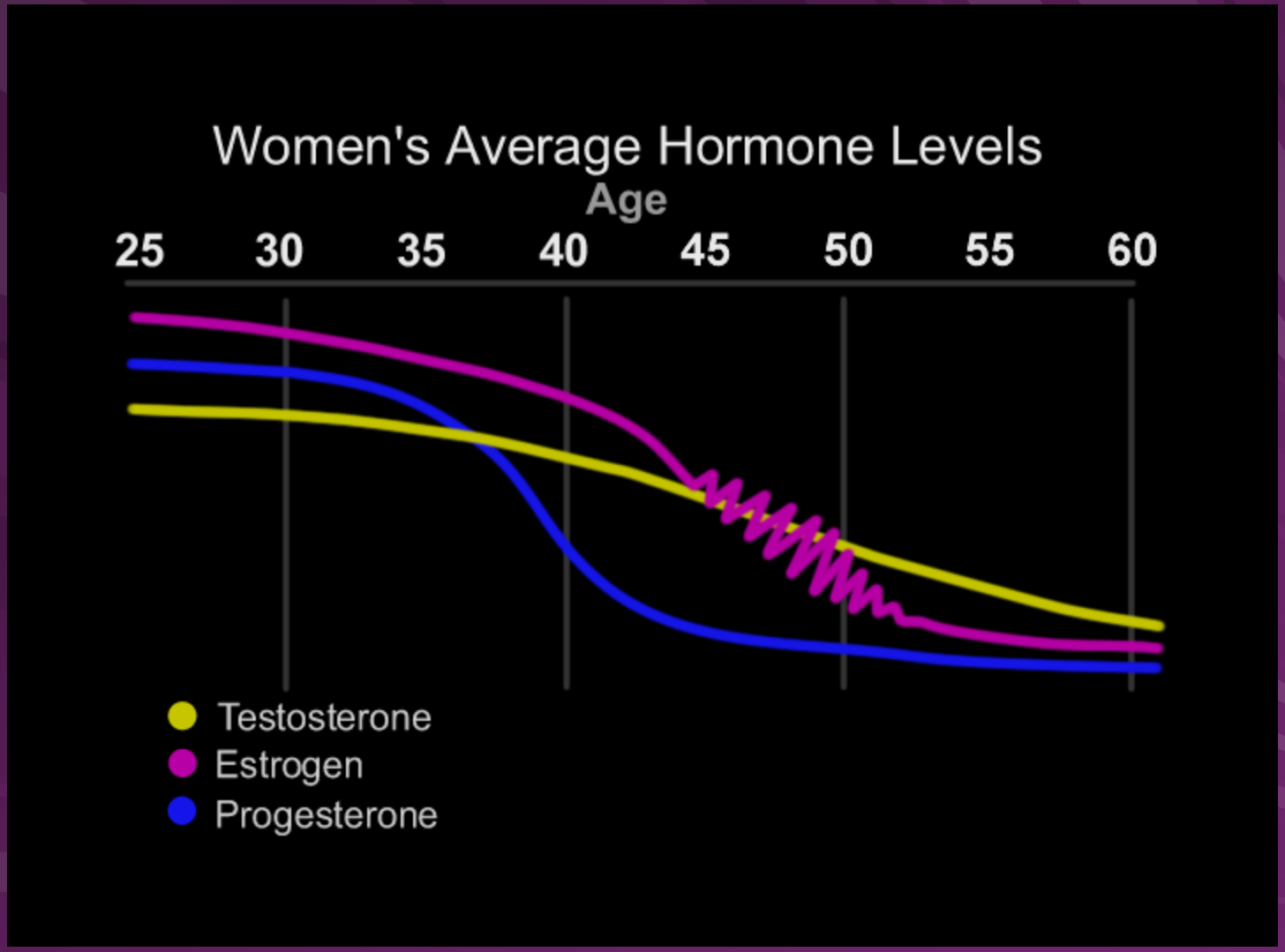
Women’s Average Hormone Levels



The Complete HORMONE makeover

Women’s Average Hormone Levels



The Complete HORMONE makeover

Estrogens

- E2 receptors are present in the amygdala and hippocampus, which influence mood and behavior
  - Genazzani AR, Lucchesi A, Stomati M, et al. Effects of sex steroid hormones on the neuroendocrine system. Eur J Cotracept Reprod Health Care. 997; 2: 63-69.
- ↑#serotonergic receptors in the brain & ↑production of serotonin
  - Kugaya A, Epperson CN, Zoghbi S, et al. Increase in prefrontal cortex serotonin 2A receptors following estrogen treatment in postmenopausal women. Am J Psychiatry. 203;160:1522-1524.
- Modulates activity of the noradrenergic system and diminishes the number and sensitivity of dopamine receptors
  - Garlow S, et al. The neurochemistry of mood disorders: clinical studies. In:Neurobiology of Mental Illness, 1999.

Progesterone

- calming, mood stabilizing effect
- modulates the brain's response to amino acid neurotransmitters that help regulate mood, sleep, cravings, etc.
- down-regulating the brain's GABA receptors. (Like Valium — except good for you!)

Nutrient Deficiencies Interfere with hormone actions

Nutrient	Hormone Action
Iodine	critical in thyroid, part of every hormone receptor
Zinc	E2, T, GH receptor
B6	fxns to clear E2 from receptor site, cofactor for NT
Calcium	Vit D
Magnesium	Nec. for phosphorylation of pyridoxine, EFAs, dopa
Methyl donors	(MSM, folic acid, DMG) needed for metabolism
Cobalt	E function
Chromium	ovarian P production
Boron	E and T

Nutrient Deficiencies Interfere with hormone actions

Drug	Nutrient Deficiency
Antibiotics: Penicillin, cephalosporins: Tetracyclines:	 B Vitamins, Vitamin K Ca, Mg, Fe, B6, Zn
NSAIDs: Aspirin & Salicylates:	Folic acid Vit C, Ca, Folic acid, Fe, B5
Oral Contraceptives	Folic acid, B1, B2, B3, B6, B12, Vit C, Mg, Se, Zn

Treatment Options

- Birth Control
  - Drospirinone (Yasmin/Yaz)
  - Nuvaring
  - Mirena IUD
- GnRH agonist (Lupron)
- Depo-Provera
- NSAIDs
- Spironolactone 100mg qd cd 15-28
- SSRIs
- Anxiolytics
- Endometrial Ablation
- BSO

Treatment Options

- Cultural attitudes & personality
- Therapeutic Lifestyle Changes
  - Stress Management
  - Aerobic exercise
  - Dietary
- 25% of women low calcium
- 90% low folate, vit E
- 50% or more have deficiency in iron, manganese, and zinc
- 50% eat < 5 fruit & vegetables/day
- 33% meals eaten outside of home
  - a 66% increase over the last decade

-The American College of Obstetricians and Gynecologists. Practice Bulletin. Management of premenstrual syndrome. *Clinical Management Guidelines No. 15.* April 2000

Treatment Options

- **Dietary Recommendations**
  - Fiber! (at least 25 g/day)
  - Flaxseed, fresh ground 1 – 2 tbsp daily
  - Avoid high fat diet but use good oils!
  - Choose Organic, free range
  - Limit Caffeine and alcohol
  - Limit refined carbohydrates

Treatment Options

Supplements

- B6 (P5P) 50 - 100 mg/d
- Calcium 600 mg bid

- Thys-Jacob S , Starkey P , Bernstein D , et al. Calcium carbonate and the premenstrual syndrome: Effects on premenstrual and menstrual symptoms . *Am J Obstet Gynecol* . 1998 ;179 :444 .
- Wyatt KM, Dimmock PW, Jones PW, et al. Efficacy of vitamin B6 in the treatment of premenstrual syndrome: Systemic review. Br Med J. 1999; 318: 1375-1381.

Treatment Options

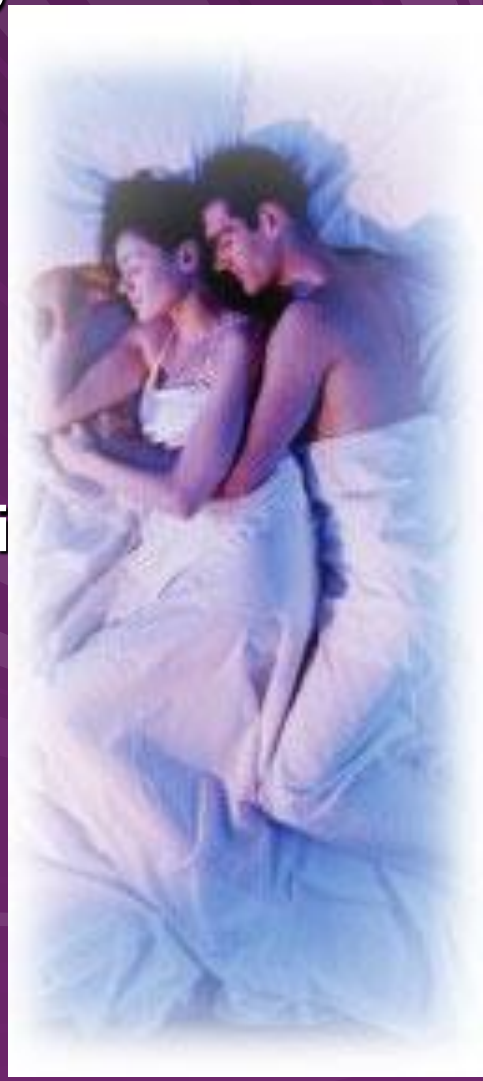
Supplements cont'd:

- Omega's, Krill, GLA 2000 – 6000 mg/d
- Magnesium 200 – 400 mg/d (Magnesium Malate)
- Vitamin E (mixed tocotrienols) 400 IU/d
- Vitamin D, check level, optimal level between 50-70
- Zinc 25 – 30 mg/d
- Manganese 1.8 mg/d
- Chaste Berry (Vitex-agnus castus) 100mg
- Gingko 80 mg tid
- Licorice
- Potassium 400 – 600 mg/d (PMS H pts)

Dennehy CE. The use of herbs and dietary supplements in gynecology: an evidence-based review. Journal of Midwifery & Women's Health. 51(6):402-9, 2006 Nov-Dec.

Treatment Options

- 5HTP 50 – 200 mg/d, L-tryptophan – PMS D
- Taurine – water balance - PMS H
- Phosphotidyl Serine 120 – 200 mg
- Phosphatidylcholine 200 mg
- Green Tea Extract 100 mg
- Calcium D Glucarate 300 mg
- Chaste Berry Extract 100mg
- Natural anti-inflammatory agents & anti-oxi
  - DIM 200 mg
  - Turmeric 50 mg
  - Resveratrol 40 mg
  - Grape Seed Extract 25mg
- Detox – ph 1 & 2 support
- Get them to sleep!
  - Inositol 700 mg
  - Melatonin 1-20 mg



MACA

- Menopause. 2008 Nov-Dec;15(6):1157-62. **Links**
  - **Beneficial effects of Lepidium meyenii (Maca) on psychological symptoms and measures of sexual dysfunction in postmenopausal women are not related to estrogen or androgen content.**
  - **Brooks NA**, **Wilcox G**, **Walker KZ**, **Ashton JF**, **Cox MB**, **Stojanovska L**.
  - School of Biomedical and Health Sciences, Victoria University, St. Albans, Victoria, Australia.
  - OBJECTIVE: To examine the estrogenic and androgenic activity of Lepidium meyenii (Maca) and its effect on the hormonal profile and symptoms in postmenopausal women. DESIGN: Fourteen postmenopausal women completed a randomized, double-blind,

CONCLUSIONS: Preliminary findings show that Lepidium meyenii (Maca) (3.5 g/d) reduces psychological symptoms, including anxiety and depression, and lowers measures of sexual dysfunction in postmenopausal women independent of estrogenic and androgenic activity.

employing up to 4 mg/mL Maca extract (equivalent to 200 mg/mL Maca). CONCLUSIONS: Preliminary findings show that Lepidium meyenii (Maca) (3.5 g/d) reduces psychological symptoms, including anxiety and depression, and lowers measures of sexual dysfunction in postmenopausal women independent of estrogenic

3,3'-Diindolylmethane suppresses the inflammatory response to lipopolysaccharide in murine macrophages.

- Cho HJ, Seon MR, Lee YM, Kim J, Kim JK, Kim SG, Park JH.
- Center for Efficacy Assessment and Development of Functional Foods and Drugs, Hallym University, Chuncheon 200-702, South Korea.

- 3,3'-Diindolylmethane (DIM), a major acid-condensation product of indole-3-carbinol, has been shown to have multiple anticancer effects in experimental models. Because recurrent or chronic inflammation has been implicated in the development of a variety of human cancers, this study examined the antiinflammatory effects of DIM and the

DIM significantly decreased the release of nitric oxide (NO), prostaglandin (PG)E2, tumor necrosis factor alpha, interleukin (IL)-6, and IL-1beta by RAW264.7 cells treated with LPS. DIM inhibited LPS-induced increases in protein levels of inducible NO synthase (iNOS), which were accompanied by decreased iNOS mRNA levels and transcriptional activity.

inflammatory responses.

Treatment Options

- Hormonal balance (Bigger is not Better)
  - Address adrenaline, cortisol, insulin, thyroid
  - Progesterone
    - 20 – 60 mg transdermal cream, qd – bid
      - cd 8 - 14 – menses
      - d 1-25
    - 50 – 400 mg oral compounded or micronized Progesterone
    - Progestin IUD insert (Mirena)
    - Vaginal suppository 20 – 50 mg
    - Injections

Progesterone & Fertility

- Progesterone peak production at luteal phase: 25-30 mg/d
- Oral Micronized P form better absorbed
- Oral P rapidly metabolized - >90%
- IM – well absorbed
- Vaginal – no liver 1st pass effect, absorbed by lymphatics
  - 1st pass through the uterus
  - 50 mg/d for pregnancy support – 1st Δ

Practice Committee of the ASRM. Progesterone Supplementation during the luteal phase and in early pregnancy in the treatment of infertility: an educational bulletin. Fertil. Steril. 2008; 89: 789-792.

Effect of oral vs transdermal hormone therapy on lipid levels in postmenopausal women

	E	E+P	TD E	TD E+P
TC	↓	↓	↓	↓
LDL	↓	↓	↓	↓
HDL	↑	(↑)	↑	(↑)
TG	↑	(↑)	↓	↓

E + P, estrogen + progestin combination.
Parentheses indicate blunted effect relative to unopposed estrogen.
Adapted from Godsland IF. Fertil Steril. 2001;75:898-915. Shulman LP, Yankov V, Uhl K. Menopause. 2002;9:195-207

TI **Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study.**

A U **Canonico M; Oger E; Plu-Bureau G; Conard J; Meyer G; Levesque H; Trillot N; Barrellier MT; Wahl D; Emmerich J; Scarabin PY**

S O **Circulation. 2007 Feb 20;115(7):840-5.**

BACKGROUND: O
postmenopausal
data have limited
AND RESULTS: W
women 45 to 70
cases with a first
cases) and 610 c
age, and admissi
(ORs) for VTE in
4.2 (95% CI, 1.5
association of VT
0.3 to 1.9 and OR
were associated
CONCLUSIONS: C
addition, our data
micronized proge
risk. If confirmed
menopausal sym
progestogens.

CONCLUSIONS: Oral but not transdermal estrogen is associated with an increased VTE risk. In addition, our data suggest that norpregnane derivatives may be thrombogenic, whereas micronized progesterone and pregnane derivatives appear safe with respect to thrombotic risk. If confirmed, these findings could benefit women in the management of their menopausal symptoms with respect to the VTE risk associated with oral estrogen and use of progestogens.

A D **Inserm Unit 780,**
94807 Villejuif Cedex, France.

- (Canonico M 2007)
- Odds ratio for VTE for oral E = 4.2
- OR for VTE fro transdermal E = 0.9
- OR for VTE for OMP = 0.7
- OR for VTE for synthetic progestin's = 3.9
- Oral but not Transdermal E assoc with incr risk of VTE.
- Synthetic progestin's may be thrombogenic, unlike OMP

Programs

- www.Cabecahealth.com/feelfabulous
- www.WomensRestorativeHealth.com
- www.SexualCPR.com/helpdoctor
- www.MightyMaca.com
- Gims@Cabecahealth.com
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