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TUCSON, ARIZONA



NEGLECTED BUT EFFECTIVE THERAPIES BASED ON PUBLISHED RESEARCH PART 2 – WOMENS HEALTH



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Relevant financial relationships in the past twelve months by presenter or spouse/partner:

Employment: N/A

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**Status of FDA devices used for the material
being presented: NA/Non-Clinical**

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constitute the subject of this presentation: NA/Non-Clinical**

**No other relevant financial relationships in the past twelve
months by presenter or spouse/partner**



LITTLE-KNOWN BENEFITS OF BIO-IDENTICAL HORMONE REPLACEMENT

Estradiol versus Cortisol...

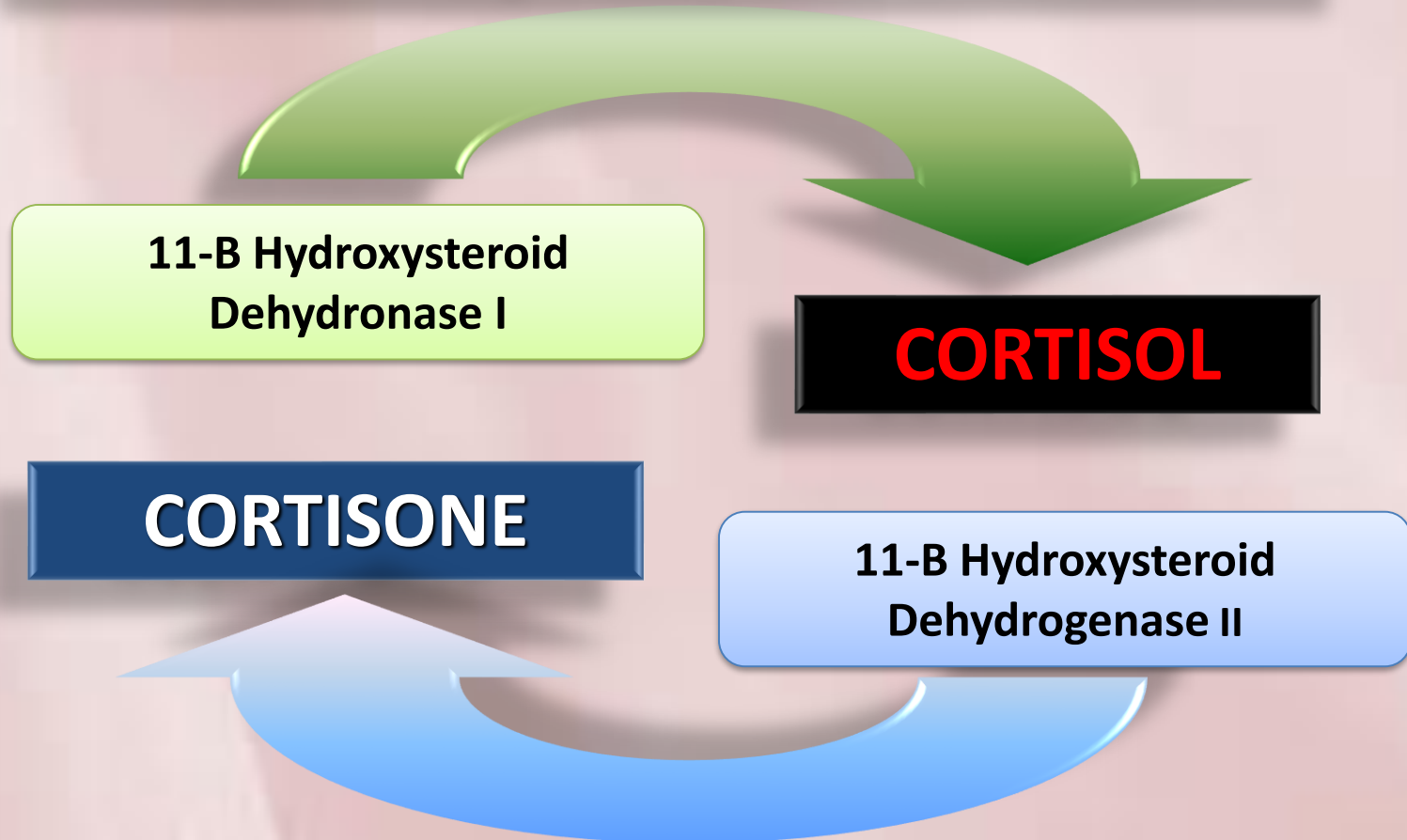


**...and Postmenopausal
Belly Fat!**

Estradiol v Cortisol

- “Estradiol down regulates 11 β -hydroxysteroid dehydrogenase 1, resulting in a reduction of tissue specific cortisol production.”
 - ✓ Cohen, Paul G. *Estradiol induced inhibition of 11 β -hydroxysteroid dehydrogenase 1: an explanation for the post-menopausal hormone replacement therapy effects.* Med Hypotheses. 2005;65(4):819

Inhibited by Estradiol and HGH



Inhibited by Licorice and Cadmium

Estradiol v Cortisol

- Klopfenstein BJ. Oregon Health and Science University, Portland, Oregon. *24-hour Cortisol Production Rates, Free Cortisol, and Intra-Abdominal Fat are Elevated in Postmenopausal Women but are Similar in Premenopausal and Postmenopausal Women Taking Hormone Replacement Therapy.*
 - ✓ Abstract of research presented at Endocrine Society annual meeting Summer 2003

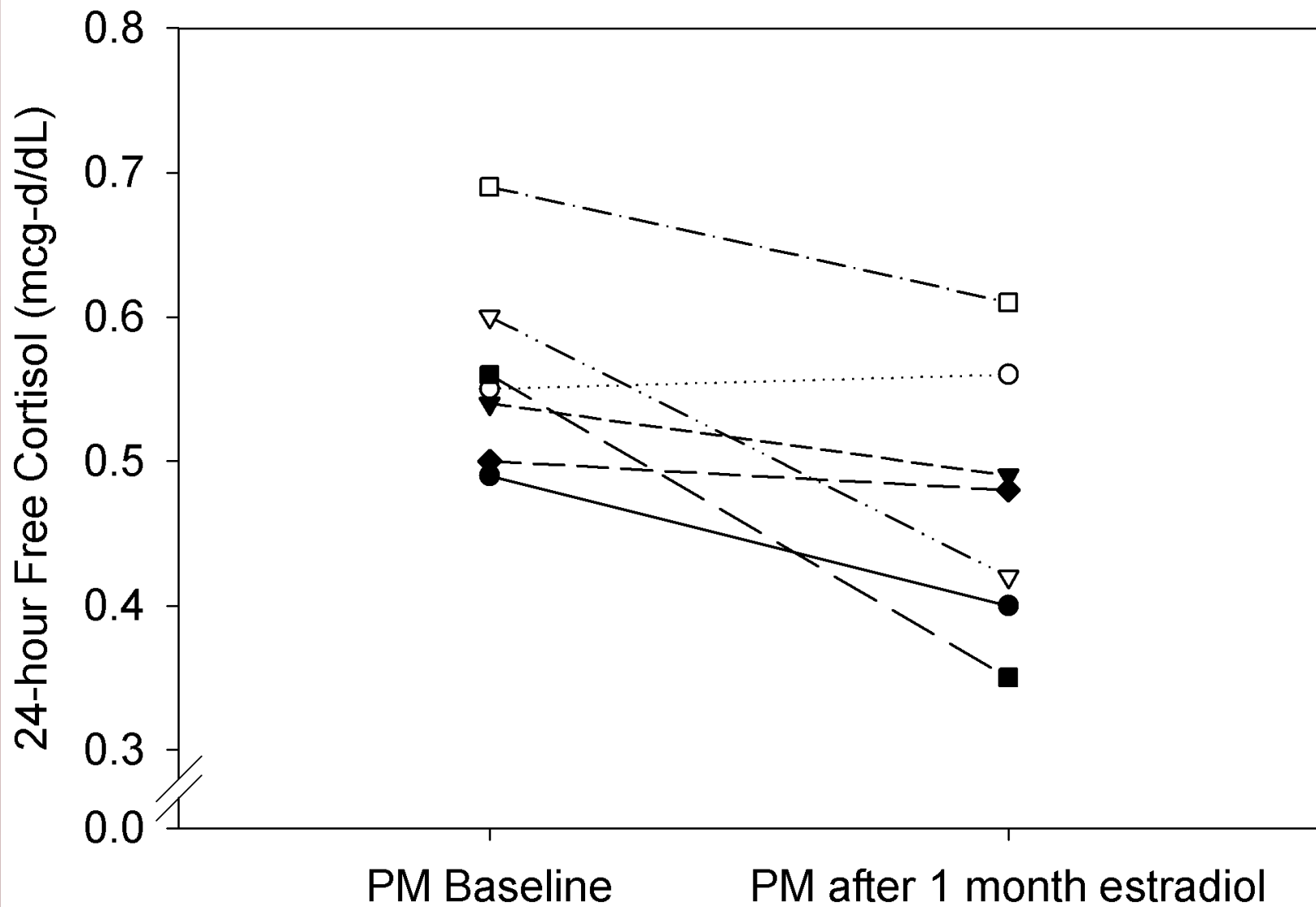
Comparison:

Premenopausal, Premenopausal with Treatment, Post Menopausal

	PRE M	PM + HRT	PM
Area Under Curve Cortisol (mg-dL/day)	6780 ± 409	7059 ± 1265	7750 ± 859
Cortisol Binding Globulin (mg-dL)	22.7 ± 1.3	28.3 ± 0.9	22.6 ± 1.6
Free Cortisol (mcg-d/dL)	0.395 ± 0.026	0.363 ± 0.029	0.540 ± 0.079
Intra Abdominal Fat (cm ²)	85 ± 16	119 ± 15	160 ± 31

Estrogen Lower → Cortisol Higher

- *“...estrogen deficiency is associated with higher cortisol production rates and elevated plasma free cortisol levels, which may contribute to development of central obesity during menopause.”*
- *“...Future studies may demonstrate a role for HRT in protection against post-menopausal increases in free cortisol and accumulation of visceral fat.”* ---Klopfenstein, ppt #7



FSH Receptors in Fat Cells

FSH Promotes Lipid Synthesis

“....the receptor of follicle-stimulating hormone (FSH), a gonadotropin that increases sharply and persistently with aging in both males and females, is functionally expressed in human and mouse fat tissues and adipocytes. Follicle-stimulating hormone was found to promote lipid biosynthesis and lipid droplet formation.....”

- ✓ Liu XM, Chan HC et al. *FSH regulates fat accumulation and redistribution in aging through the Gai/Ca²⁺/CREB pathway* Aging Cell (2015) 14, pp409–420**

FSH Stimulates Obesity and Osteoporosis

- *“A polyclonal antibody that targets the β -subunit of the pituitary hormone follicle-stimulating hormone (Fsh) increases bone mass in mice...this antibody sharply reduces adipose tissue in wild-type mice...The antibody also causes profound beiging, increases cellular mitochondrial density, activates brown adipose tissue and enhances thermogenesis...Our studies uncover opportunities for simultaneously treating obesity and osteoporosis.*
 - ✓ Liu P, Yaoting J, et al. *Blocking FSH induces thermogenic adipose tissue and reduces body fat* Nature 2017 Jun 1:546(7656);107-112

Melatonin Versus Fat

***“...small doses of melatonin (1 and 3 mg/d) have beneficial effects...reduced fat mass and borderline significantly increased lean mass in postmenopausal women...may be explained by a melatonin-driven increase in osteogenesis resulting in decreased adipogenesis...melatonin may be an interesting therapeutic agent for future treatment strategies against osteoporosis and age-related changes in body composition.*”**

Melatonin Versus Fat

- **Amstrup AK, Sikjaer T, et al *Reduced fat mass and increased lean mass in response to 1 year of melatonin treatment in postmenopausal women: A randomized placebo-controlled trial.* Clinical Endocrinology (2016) 84:342–347**

Estrogen and Female Lung Function

- Massaro D, Massaro GD. *Estrogen regulates pulmonary alveolar formation, loss, and regeneration in mice*, Am J Physiol Lung Cell Mol Physiol 2004;287(6):L1,154-L1,159
- Massaro D, Massaro GD. *Toward therapeutic pulmonary alveolar regeneration in humans*, Proc Am Thorac Soc 2006;3(8):709-712

Estrogen and Female Lung Function

- Massaro GD, Mortola JP, Massaro D. *Sexual dimorphism in the architecture of the lung's gas-exchange region*. Proc Natl Acad Sci U.S.A. 1995;92(4):1,105-1,107
- Massaro GD, Mortola JP, Massaro D. *Estrogen modulates the dimensions of the lung's gas-exchange surface area and alveoli in female rats*. Am J Physiol 1996;270(1 Pt 1): L110-L114

Menopause, Lung Function, COPD

- Estrogen decline during “normal aging” results in loss of alveoli; menopause further accelerates loss of lung surface area which reduces oxygen-carbon dioxide exchange and makes tissue oxygenation less efficient.
- Among “never-smokers” who develop COPD, female/male ratio is 6-8/1.

Menopause, Lung Function

- “...Lungs isolated from old mice (24 months old, estrogen-deficient) demonstrated decreased lung volume and decreased alveolar surface area.... Estrogen replacement restored lung volume, alveolar surface area, and alveolar wall thickness to that of a young mouse.”
 - ✓ Glassberg MK(1), Choi R, et al. *17 β -estradiol replacement reverses age-related lung disease in estrogen-deficient C57BL/6J mice*. Endocrinology. 2014 Feb;155(2):441-8

Women's Vocal Quality

- In the “early days” of BHRT 1982-1985, many letters and ‘phone calls were received from choir directors, “voice coaches, and from women who’d recently started BHRT telling us that their voices were “back to normal” after using BHRT for a few weeks.

Estrogens for Breast Cancer Survivors?

- **Estriol: Stimulates $Er\beta$ only.**
 - ✓ *In brain, stimulates receptors for “mood, attitude, affect”.*
- **2-methoxyestradiol: Pronounced anti-carcinogenic effect.**
 - ✓ *At present, receptor for this molecule not known , although it’s said to be within the “tubulin system”*

Cancer Survivor #1

24-Hour Urine Results

Steroid	Excreted in Ug/24 Hr	Ref Range (Luteal Phase)
Estriol	59.2	6.1 – 32.4
2-Methoxyestradiol	4.1	0.1 – 2.2

- **51 years old**
- **Patient using 1 milligram transmucosal Estriol, days 1-25 and 200 micrograms transmucosal 2-Methoxyestradiol, days 1-25**

Cancer Survivor #2

24-Hour Urine Results

Steroid	Excreted in Ug/24 Hr	Ref Range (Luteal Phase)
Estriol	119.5	6.1 – 32.4
2-Methoxyestradiol	28.3	0.1 – 2.2

- **62 years old**
- **Patient taking 3 mgs transmucosal Estriol, days 1-25 and 3 mgs transmucosal 2-Methoxy-estradiol, days 1-25**

Testosterone and Dry Eyes

- “...the meibomian gland is an androgen target organ..”
- “...androgen deficiency, due to an attenuation of...synthesis...during Sjogren’s syndrome, menopause, aging...will lead to evaporative dry eye.”
 - ✓ Sullivan DA et al. *Androgen Deficiency, Meibomian gland dysfunction, and evaporative dry eye*. Ann NY Acad Sci 2002; 966:211-222

Testosterone and Dry Eyes

- **“Transdermal delivery of testosterone appears to be a safe and effective treatment for dry eye....Post-menopausal females perceived the greatest relief of symptoms from the treatment, while males had the least benefit.”**
 - ✓ **Connor CG. *Treatment of Dry Eye with a Transdermal 3% Testosterone Cream*. Invest Ophthalmol Vis Sci 2003;44**

Oxytocin and Muscle

- “...systemic administration of oxytocin rapidly improves muscle regeneration by enhancing aged muscle stem cell activation/proliferation through activation of the MAPK/ERK signalling pathway.”
 - ✓ Elabd C, Cousin W, et al *Oxytocin is an age-specific circulating hormone that is necessary for muscle maintenance and regeneration*. Nat Commun 2014 Jun 10;5:4082

As Oxytocin also Regenerates and Maintains Muscle Mass:

- **Always check oxytocin along with Testosterone, especially for women; particularly important if early signs of muscle mass shrinkage.**
- **Paradoxically, oxytocin is harmless—never harms infant or mother during childbirth—but is only available on prescription.**

DHEA and Women: Cardiovascular and “All Cause” Mortality

- **Shufelt C et al. *DHEA-S Levels and Cardiovascular Mortality: Results from the National Institutes of Health—National Heart, Lung, and Blood Institute (NHLBI)-Sponsored Women’s Ischemia Syndrome Evaluation (WISE)* J Clin Endocrinol Metab. 2010 Nov;95(11):4985-92**

DHEA and Women: Cardiovascular and “All Cause” Mortality

- “Among postmenopausal women with coronary risk factors under-going coronary angiography for suspected myocardial ischemia, *lower DHEA-S levels were linked with higher CVD mortality and all-cause mortality.*”

“Local” DHEA and Female Sexuality

“The objective of this study was to provide evidence that the transformation of DHEA into both androgens and/or estrogens locally in cells of the three layers of the vagina (epithelium, lamina propria, and muscularis) would have effects of greater impact, including effects on sexual function, than only effects on superficial epithelial cells as achieved with estrogens”

-See Citation #1

“Local” DHEA and Female Sexuality

“By a local action in the vagina, DHEA applied daily at doses at which serum steroids remain well within normal postmenopausal values exerts relatively potent beneficial effects on all four aspects of sexual dysfunction. Such data indicate that combined androgenic/estrogenic stimulation in the three layers of the vagina exerts important beneficial effects on sexual function in women without systemic action on the brain and other extravaginal tissues.”

-See Citation #1

Trial Results:

- Compared with placebo:
 - ✓ Arousal/ sensation was improved by 68% ($p=0.006$)
 - ✓ Arousal/lubrication by 39% ($p = 0.014$)
 - ✓ Orgasm improved by 75% ($p = 0.047$)
 - ✓ Dryness during intercourse by 57% ($p = 0.0001$)
- *“...the present data clearly show that intravaginal DHEA is a very efficient treatment for FSD without significant systemic exposure...”*

-See Citation #1

DHEA and Female Sexuality

- *“Daily oral DHEA therapy at the dose of 10 mg.... provided a significant improve-ment in comparison with vitamin D in sexual function and in frequency of sexual intercourse in early postmenopausal women.”*
 - ✓ Genazzani AR, Stomati M, Valentino V, Pluchino N, Pot E, Casarosa E, Merlini S, Giannini A, Luisi M. *Effect of 1-year, low-dose DHEA therapy on climacteric symptoms and female sexuality.* Climacteric. 2011 Dec;14(6):661-8

DHEA and Female Sexuality

- “In sum, increases in mental and physical sexual arousal ratings significantly increased in response to an acute dose of DHEA in postmenopausal women.”
 - ✓ Hackbert L, Heiman JR. *Acute dehydroepiandrosterone (DHEA) effects on sexual arousal in postmenopausal women.* J Womens Health Gen Based Med. 2002 Mar;11(2):155-62

DHEA, Other Benefits

- Baulieu EE, Thomas G et al. *Dehydro-epiandrosterone (DHEA), DHEA sulfate, and aging: contribution of the DHEAge Study to a socio-biomedical issue.* Proc Natl Acad Sci U S A. 2000 Apr 11;97(8): 4279-84

DHEA, Other Benefits

*“[280] healthy...women and men 60-79 years old...
DHEA, 50 mg, or placebo, orally, daily...a year...
double-blind, placebo-controlled study...small increase
of testosterone and estradiol...particularly in
women...Bone turnover improved...in women >70
years old...significant increase in most libido para-
meters...in these older women. Improvement of... skin
status...particularly in women...hydration, epidermal
thickness, sebum production, and pigmentation.”*

--See Citation #2

DHEA: Tissue-Specific Effects

- **Androgenic:** Bone formation(a), Sebaceous gland stimulation(a), mammary gland inhibition(a), muscle mass increase(a), improved libido(a,b,c)
- **Estrogenic:** Vaginal mucosa maturationa Insulin resistance decreased (a,b)
- **No effect:** Endometrium(a)
 - a.** Demonstrated in postmenopausal women.
 - b.** Possibly also androgenic.
 - c.** Possibly also estrogenic.

Bonus Info: Zestra for Women

- “Zestra for Women is a botanical feminine massage oil...applied to the vulva... randomized, double-blinded, crossover study... in 10 women with and 10 women without female sexual arousal disorder (FSAD)”...

--See Citation #3

Bonus Info: Zestra for Women

- *...Both normal and FSAD women showed statistically significant improvements, relative to placebo, in level of arousal, level of desire, satisfaction with arousal, genital sensation, ability to have orgasms, and sexual pleasure.”*

--See Citation #3

Bonus Info: Zestra for Women

- **Contains: borage seed oil, evening primrose oil, angelica extract, coleus forskohlii extract, theobromine, ascorbyl palmitate, tocopherol, and natural flavor.**



FORGOTTEN THERAPIES FOR WOMEN'S HEALTH

**With Information from 43 Years
of Reading, Listening and
Observing!**

Reversing “Gestational” Diabetes



Reversing “Gestational” Diabetes

- **14 pregnant women were diagnosed with gestational diabetes by the standard glucose tolerance test. All took vitamin B6 (as pyridoxine) 100 milligrams daily for two weeks, after which repeat glucose tolerance testing found that 12 of 14 (86%) were normal!**

Reversing “Gestational” Diabetes

- **Bennink H, Schreurs W. *Improvement of oral glucose tolerance in gestational diabetes by pyridoxine*. Brit Med J 1975; 3(5974):13-15**

Reversing “Gestational” Diabetes

- 13 women with late pregnancy diagnosed gestational diabetes had glucose tolerance tests (with insulin measurements) before and after taking vitamin B₆ (as pyridoxine) 100 milligrams daily for 2 weeks.
- All 13 women (100%) had significant improvements in their glucose tolerance tests, despite an unchanged or lowered plasma insulin level.

Reversing “Gestational” Diabetes

- Spellacy WN, Buhi WC Birk SA. *Vitamin B6 treatment of gestational diabetes mellitus: Studies of blood glucose and plasma insulin. Am J Ob Gyn 1977; 127(6):599-602*

Gestational Diabetes, Effects of High Estrogens

- In susceptible women, high estrogen suppresses weak pyridoxine-dependent enzymes, which shifts tryptophan metabolic pathways towards production of excess xanthurenic and kynurenic acids.
 - ✓ Wolf, H et al. *Effect of natural oestrogens on tryptophan metabolism: evidence for interference of oestrogens with kynurinease*. Scand J Clin Lab Invest (1980);40(1):15-22

One Effect of Excess Xanthurenic Acid:

- Excess xanthurenic acid binds and inactivates insulin; blood sugar rises, resulting in “gestational” (high estrogen) diabetes.
 - ✓ Kotake Y. et al. *The physiological significance of the xanthurenic acid-insulin complex* J Biochem 1975;77:685-687

Reversing “Gestational” (High-Estrogen) Diabetes

- **Pyridoxine (especially pyridoxal-5-phosphate) restores normal activity of weak pyridoxine-dependent enzymes, normalizing tryptophan metabolism, restoring normally low levels of xanthurenic and kynurenic acid, reversing “gestational” diabetes.**

Additional Data:

- **High urinary xanthurenic acid was considered diagnostic for Vitamin B6 deficiency in the 1940s and 1950s.**
- **Recommend magnesium whenever recommending Vitamin B6.**

Eliminating Menorrhagia

- Seventy-one women with menorrhagia had lower serum vitamin A than healthy women.
- Forty took vitamin A, 25,000 IU twice a day for fifteen days.
- Menstruation normalized in 23 (57.5%)
- There was substantial improvement in another 14 (35%).
- Overall, 37 of 40 (92.5%) had complete relief or significant improvement of menorrhagia.

--See Citation #4

Menstrual Clotting

- **Even very heavy, painful menstrual clotting decreases gradually to none at all in 4 to 6 months time with 10-15 milligrams oral vitamin K daily.**
 - ✓ **(Has been successful with K1, MK4)**

Another Physiologic Way to Eliminate Menstrual Cramps

- **40 years of clinical observation:**
 - ✓ **Cod liver oil 1 tablespoonful BID (with mixed tocopherols), taper as cramps disappear!**

Hair Loss (“Thinning”) or Poor Quality Fingernails

- **Nearly always caused by malabsorption secondary to significant gastric hypochlorhydria and/or gluten-gliadin sensitivity.**
- **Treatment of the cause of malabsorption combined with appropriate supplementation reverses and corrects these problems.**

HCG and Endometriosis

- “Three months of HCG therapy led to a highly significant reduction of endometriosis-related pain ($p < 0.001$) and to improvement of disease related parameters such as:
 - ✓ *Sleeplessness* ($p < 0.001$),
 - ✓ *Irritability* ($p < 0.001$),
 - ✓ *Overall discomfort* ($p < 0.001$),
 - ✓ *Depressive moods* ($p < 0.001$) and
 - ✓ *Painful defecation* ($p = 0.01$).

HCG and Endometriosis

- “Dyspareunia and dysmenorrhea also clearly improved (both $p < 0.001$), though HCG did not lead to significant reduction of dysuria ($p = 0.66$). Prolonged therapy with HCG for up to 12 months (mean: 4.42 months) did not lead to reduction of the beneficial effect.”
 - ✓ HCG dose 1500 IU to 5000 IU once or twice weekly for three months.

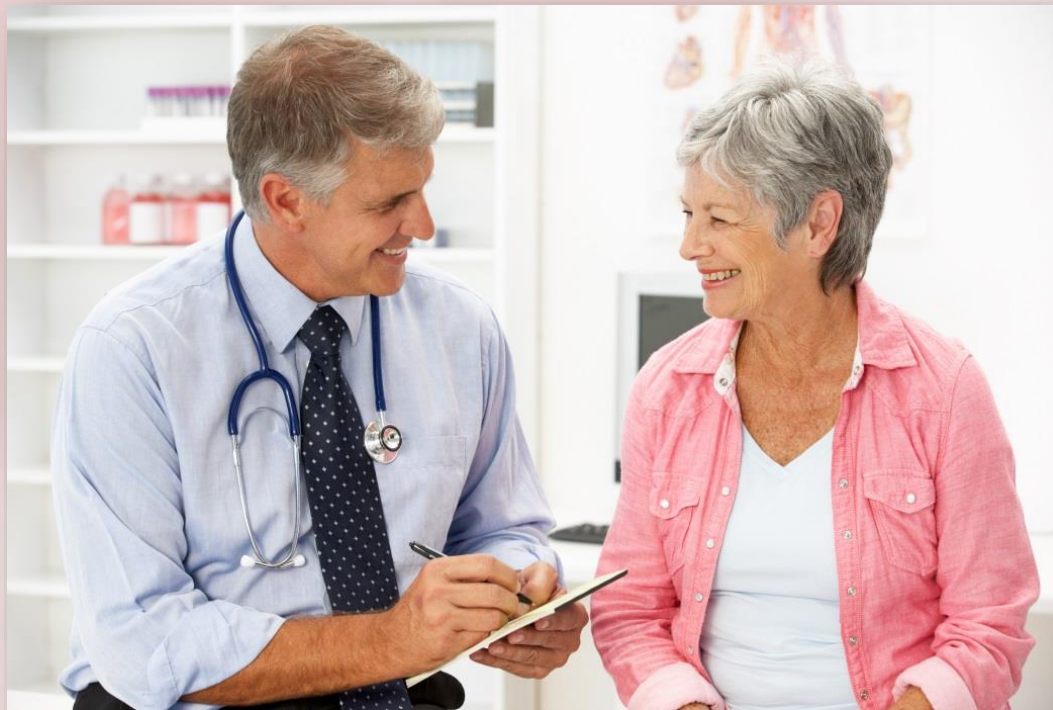
--See Citation #5

Endometriosis May Be Auto-immune!

- ***“207 women with chronic pelvic pain caused by endometriosis were placed on a gluten elimination diet for twelve months. One hundred fifty six (75%) of the women had significant pain relief; 51 (25%) did not. None had worsening of pain...100% reported ‘considerable increase’ in vitality, social functioning, and mental health.”***

--See Citation #6

Auto-Immunity: Treatment With Estriol



Estriol Inhibits T Cell Transmigration, Promotes Th2

- **“Estriol significantly inhibited T cell transmigration...Estriol was also found to alter the cytokine profile of T cells toward Th2 phenotype ...the inhibitory effects of estriol on T cells were not antigen-dependent... estriol is a potent regulator for T cell functions....”**
 - ✓ **Zang YC, Halder JB et al. *Regulatory effects of estriol on T cell migration and cytokine profile: inhibition of transcription factor NF-kappa B*. J Neuroimmunol. 2002 Mar;124(1-2):106-14**

Estriol Induces Tolerogenic Dendritic Cells

- **“Our results showed that E3 generates tolerogenic DCs [dendritic cells], which protect against the inflammatory autoimmune disease EAE. Targeted generation of tolerogenic DCs with immunomodulatory therapeutics, such as E3, has potential applications in the treatment of numerous autoimmune and chronic inflammatory diseases.”**
 - ✓ **Papenfuss TL, Powell ND, et al. *Estriol Generates Tolerogenic Dendritic Cells In Vivo That Protect against Autoimmunity*. J Immunol 2011; 186: 3346–3355**

Estriol Improves Autoimmunity in Multiple Sclerosis 1

- *“As compared with pretreatment baseline, relapsing remitting patients treated with oral estriol (8 mg/day) demonstrated significant decreases in delayed type hypersensitivity responses to tetanus, interferon-gamma levels in peripheral blood mononuclear cells, and gadolinium enhancing lesion numbers and volumes on monthly cerebral magnetic resonance images.”*

Estriol Improves Autoimmunity in Multiple Sclerosis 2

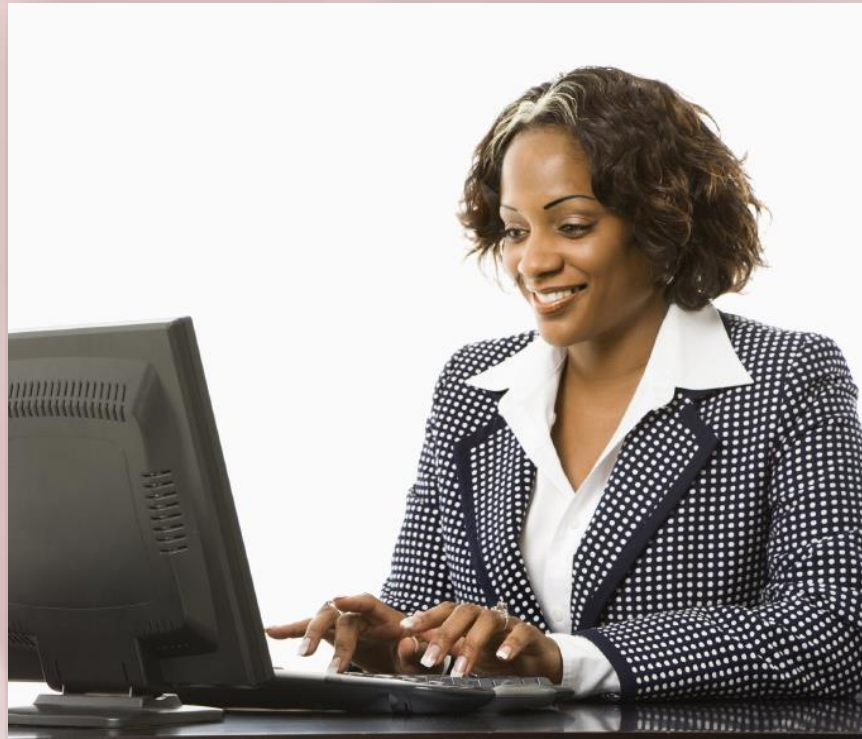
- ***“When estriol treatment was stopped, enhancing lesions increased to pretreatment levels. When estriol treatment was reinstituted, enhancing lesions again were significantly decreased...This novel treatment strategy of using pregnancy doses of estriol in multiple sclerosis has relevance to other autoimmune diseases that also improve during pregnancy.”***

--See Citation #7

Estriol: A Little Known Fact

- Pre- and post-menopausal women were given infusions of radioactively labeled estriol. Very rapid disappearance of estriol from serum was confirmed by the very rapid disappearance of radioactivity from serum.
 - ✓ Longcope C. *Estriol production and metabolism in normal women* J Steroid Biochem 1984 Apr;20(4B):959-62

HCG and Auto-Immunity



HCG Induces Female, Not Male, Suppressor T Cells

- *“...hCG in physiologic retroplacental concentration has been shown to induce human female lympho-cytes which suppress the proliferation of B cells... hCG did not induce cells capable of suppressing...B cell proliferation in lymphocyte from males...”*
 - ✓ Fuchs T et al. *Sex-dependent induction of human suppressor T cells by chorionic gonadotrophin. J Repro Immunol 1982;4:185-190*
 - ✓ **IMPLICATIONS...hCG FOR AUTOIMMUNE WOMEN**

HCG Improves Immune Tolerance

- *“...(In a) mouse model of disturbed fetal tolerance... hCG increased regulatory T cell (“T-reg”) frequency in vivo and their suppressive activity in vitro. In females having spontaneous abortion, hCG provoked not only an augmentation of T-reg numbers, but also normalized fetal abortion rates....hCG also retained dendritic cells in a tolerogenic state”.*
 - ✓ Schumacher A et al. *Human Chorionic Gonadotrophin as a Central Regulator of Pregnancy Immune Tolerance.* J Immunol 2013;190:2650-2658

HCG and Auto-Immunity

- *“hCG has the capacity in mice of inducing lymphocytes which are subsequently competent to depress a polyclonal antibody response induced by different B cell mitogens.”*
 - ✓ Fuchs T, Hammarström L et al. *“In vitro induction of murine suppressor T-cells by human chorionic gonadotropin”* Acta Obstet. Gynecol. Scand. 59(4), 355–359 (1980)

HCG and Auto-Immunity

- Bansal AS, Shabana A. *“Mechanism of human chorionic gonadotrophin mediated immuno-modulation in pregnancy.”* Expert Rev Clin Immunol 2012;8(8),747–753

HCG and Auto-Immunity

- **“Human chorionic gonadotrophin (hCG) has a profound ability to alter maternal immune function with a view to promoting tolerance to the haploidentical fetus.”**
- **“This involves increasing T-reg recruitment and activity at the feto–maternal interface and a down-regulation of Th1 and Th17 activity.”**
- **“hCG also alters dendritic cell activity via an upregulation of indoleamine dioxygenase function that favourably skews T-cell tolerance.”**

CITATIONS

**Referenced on #s 29-31, 35, 37,
38, 50, 55, 56 and 61**

Citation #1, DHEA

- Labrie F et al. *Effect of intravaginal dehydroepiandrosterone (Prasterone) on libido and sexual dysfunction in post-menopausal women.* Menopause 2009, Vol. 16(5):923-930

Citation #2

DHEA, Other Benefits

- **Labrie F, Luu-the V et al. *Endocrine and Intracrine Sources of Androgens in Women: Inhibition of Breast Cancer and other roles of Androgens and Their Precursor Dehydro-epiandrosterone.* Endo Rev 2003;24:152-182**

Citation #3

Zestra for Women

- Ferguson DM et al. *“Randomized, placebo-controlled, double blind, crossover design trial of the efficacy and safety of Zestra for Women in women with and without female sexual arousal disorder.”* J Sex Marital Ther 2003; 29(Suppl 1):33-44

Citation #4

Eliminating Menorrhagia

- **Lithgow DM, Politzer WM. *Vitamin A in the treatment of menorrhagia*. S Afr Med J 1977;51:191-193**

Citation # 5

HCG and Endometriosis

- Huber AV, Johannes C. Huber JC, et al. *Systemic HCG treatment in patients with endometriosis: A new perspective for a painful disease.* Wien Klin Wochenschr 2004;116/ 24:839-843

Citation #6

Gluten Elimination and Endometriosis

- Marziali M, Vemza M, Lazzaro S et al. *Gluten-free diet: a new strategy for management of painful endometriosis related symptoms?* Minerva Chirurgica 2012;67(6):499-504

Citation #7

Estriol Improves Autoimmunity in Multiple Sclerosis

- **Sicotte NL, Liva SM et al. *Treatment of multiple sclerosis with the pregnancy hormone estriol*. Ann Neurol. 2002 Oct;52(4):421-8**

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