Climacteric and Pain or: Doctor I'm Getting Old

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Climacteric

- A critical period or event.
- Physiology. a period of decrease of reproductive capacity in men and women, culminating, in women, in the menopause.

Female Climacteric/ Menopause:

- End of the Woman's reproductive life.
- Ovaries cease to respond to pituitary gonadotrophin stimulation
- Absence of menses for 1 year.

Menopausal Symptoms

- Hot Flashes
- Sleep disturbance
- Mood Changes
- Vaginal dryness, frequency
- Weight gain
- Loss of libido
- Memory changes, brain fog
- Dry eyes, hair & itchy skin
- **Loss of muscle mass & strength**
- **Joint & Muscle stiffness and soreness**

Serum Testing

- FSH, LH, Estradiol, Progesterone
- TSH, fT4, fT3, rT3, thyroid antibodies
- Testosterone, Free Testosterone
- DHEAS
- Cortisol a.m., p.m.
- Vitamin D
- CBC, ferritin, Vitamin B12
- LFTs, Cholesterol, CRP, ANA, RF

Serum Hormone Testing

Measurement of serum hormone levels can be potentially misleading because hormone levels do not always predict therapeutic effect (thus the recommendation to use symptoms as the clinical end point for dosing).

Kuhl H. Pharmacology of estrogens and progestogens: influence of differentroutes of administration. Climacteric. 2005;8(suppl 1):3-63.

North American Menopause Society. Estrogen and progestogen use inpostmenopausal women: 2010 position statement of The North AmericanMenopause Society. Menopause. 2010;17(2):242-255.

Salivary Hormone Testing

Poor reproducibility and large collection and assay variability even for a given individual, depending on the time of day, diet, salivary flow, and hormone being tested.

Bioidentical Hormone Therapy: A Review of the Evidence *M. Cirigliano. Journal of Women's Health. June 2007*

Salivary Cortisol

- Salivary cortisol is a measure of active free cortisol and follows the diurnal rhythm of serum or plasma cortisol.
- Has been used extensively as a biomarker of stress in a research setting, especially in studies examining psychological stress with repeated measurements.

Inder WJ, et.al. Clin Endocrinol (Oxf) 2012 Nov;77(5):645-51. ***Measurement of salivary cortisol in 2012 - laboratory techniques and clinical indications.***

Population studies

- OA: worse in men than women before 50 y.o. After 50 worse in women. Gap widens with advancing age. Studies show strong support for beneficial effect of estrogen in women for O.A.

P. Richette, Estrogens, cartilage, and osteoarthritis Joint Bone Spine, 70 (2003), pp. 257–262

- Study, conducted on a large unselected population, did not demonstrate association between sex hormones and chronic pain.

Macfarlane TV, Sex hormonal factors and chronic widespread pain: a population study among women. Rheumatology (Oxford). 2002 Apr;41(4):454-7.

Estrogen and Pain

Estrogen influences inflammation and spinal processing of nociceptive/pain input through:

- Inhibition of microglial activation which inhibits production of inflammatory mediators including prostaglandin E2 and nitric oxide synthase.
- Opioid pain fibres in the CNS.
- Both estrogen receptors, alpha and beta, are found in normal cartilage.

Coleman RE, Aromatase inhibitor-induced arthralgia: clinical experience and treatment recommendations. Cancer Treat

Estrogen and OA

- In ovariectomized rats, estrogen replacement prevented the cartilage breakdown caused by interleukin-1b.
- Estrogens may decrease the acceleration in subchondral bone remodeling in osteoarthritis.
- An estrogen receptor has been shown in synoviocytes.
- Physiological doses of HRT are protective and higher dosages are deleterious.

P. Richette, Estrogens, cartilage, and osteoarthritis Joint Bone Spine, 70 (2003), pp. 257–262

Integrative Hormone Health Focus on Pain

Diet and Nutrition :

- Whole foods diet
- Gluten
- Food Intolerance panel

Exercise and Fitness/Physical Activity

- Yoga, Tai Chi
- Strength Training
- Sports Medicine

Integrative Hormone Health Focus on Pain

Stress Management:

- Listening, coaching, counselling psychotherapy
- Breathing, meditation, guided imagery, hypnotherapy
- Sleep hygiene

Supplements and Herbal approaches:

- Fish oils, Arnica Gel, Cpsaicin, Tumeric, Ginger, Boswellia, Glucosamine, Chondoitin, Cats Claw, Devils Claw, SAMe, Willow

Integrative Hormone Health Focus on Pain

- TCM, acupuncture
- Physiotherapy
- Massage
- Chiropratic
- Osteopathy
- Energy Therapies

Hormones Replacement/Restoration

- Which kind? Synthetic vs Bio-identical
- Which route? Oral vs Transdermal/Transmucousal.
- Pharmaceutical/proprietary vs Compounded?
- What formulation? Estradiol vs Estriol. Transdermal Progesterone vs Oral Progesterone

But First a Review

- The *ERa* - endometrium, breast cancer cells, ovarian stroma cells, and the hypothalamus.
- *Erβ* - kidney, brain, bone, heart, skin, breast, intestinal mucosa, prostate, and endothelial cells.
- 17-*β*-Estradiol binds equally well to both receptors.
- Estrone binds preferentially to the alpha receptor.
- Estriol, and genistein to the beta receptor
- Estradiol: Estriol activity 80:1.

CEE vs Estriol; Breast Cancer Risk

- CEE are down-regulators of ER-beta potentially increasing carcinogenic properties and induce DNA damage in breast cells.
- Estriol binds preferentially to estrogen receptor-beta which inhibits breast cell proliferation and may inhibit estradiol binding.

The bioidentical hormone debate: are bioidentical hormones (estradiol, estriol, and progesterone) safer or more efficacious than commonly used synthetic versions in hormone replacement therapy? Holtorf K. Postgrad Med. 2009 Jan;121(1):73-85

Progestins vs. Progesterone; Effects on breast and breast cancer cells.

- Synthetic progestins –anti-apoptotic, may significantly stimulate breast cell proliferation, increase conversion of weaker endogenous estrogens to more potent ones.
- Progesterone inhibits breast cell proliferation, down regulates estrogen receptor-1, induces breast cancer cell apoptosis and proliferation and increases conversion of more potent endogenous estrogens to weaker. **The bioidentical hormone debate: are bioidentical hormones (estradiol, estriol, and progesterone) safer or more efficacious than commonly used synthetic versions in hormone replacement therapy?** Holtorf K. Postgrad Med. 2009 Jan;121(1):73-85

Progestins vs. Progesterone; Effects on Cardiovascular Risk.

- MPA decreases HDL, increases coronary artery vasoconstriction and raises BP.
- Progesterone has either no effect or mild increase in HDL (with estrogen use),decreases blood pressure in hypertensives and reduces cornary artery spasm.

The bioidentical hormone debate: are bioidentical hormones (estradiol, estriol, and progesterone) safer or more efficacious than commonly used synthetic versions in hormone replacement therapy? Holtorf K. Postgrad Med. 2009 Jan;121(1):73-85

Definition of Bioidentical Hormones (BH)

- The Endocrine Society has defined bioidentical hormones as "compounds that have exactly the same chemical and molecular structure as hormones that are produced in the human body."
- They are not "natural" they are sourced from wild yam and soy and chemically altered in a lab to become BH.

Oral vs Transdermal Estrogens

- Oral estrogens elevate CRP, TGs and thrombogenic proteins.

- Transdermal preparations bypass the liver and do not exert this effect.

Considerations in the choice of oral vs. transdermal hormone therapy: a review. Minkin MJ. J Reprod Med. 2004 Apr;49(4):311-20.

Oral vs Transdermal Progesterone

- Data on potential benefits of transdermal bioidentical progesterone remain inconsistent.
- The "first-pass" liver effect, which is responsible for metabolizing approximately 90% of progesterone ingested, creates metabolites which helps induce and maintain sleep.

Cost Comparison of Pharmaceutical vs Compounded BHRTs

- Estrogel, 17-β-Estradiol - 1.5mg/2.5 gms(2 pumps); 80g(1bottle) costs $82.37/60 days vs. compounded Estradiol vaginal cream 0.75mg/**0.25 ml** $63.74/60 day.
- For Prometrium 100mgs, the cost is $167.91/100 caps vs. compounded progesterone 100mg caps $112.61/100 caps.

Compounded BHRTs

- Compounding is the method of preparing customized medications to help meet unique physician and patient needs e.g. can add testosterone into estrogen cream.
- Important to work with a pharmacist who is properly trained in compounding, who has properly trained technicians and has a dedicated sterile area to work in.
- Delivery systems need to be accurate in terms of the amount and dosage of medication dispensed.

Compounded BHRTS Dosage Forms

- Capsules- regular and sustained release
- Transdermal Creams and Gels
- Vaginal creams/suppositories
- Lozenges/Sublingual medications

Dosaging Considerations

- Estrogen: Transdermal vs Transvaginal/ Estradiol vs Estriol.
- Progesterone: transdermal vs oral/ ?with hysterectomy?
- Cycling vs continuous

Popular formulations with Antiaging Community:

Biest 80/20 1.25-2.5 mgs = Estriol 1-2mgs and Estradiol .25 -.5mgs and progesterone 20-40mgs transdermally OD-BID.

Dosaging Considerations

My standard formulation:

Estradiol .75mgs/Estriol .15mgs/pump transmucosal cream apply 1 pump to vaginal/labial area. (Can be a.m. or p.m. depending on lifestyle issues).

Progesterone 100mgs capsule 1 qhs.

- Can be adjusted based on patients preferences and response/ side effects.

Women's Health Initiative Study:

" *The WHI is the first randomized trial to directly address whether estrogen plus progestin has a favorable or unfavorable effect on CHD incidence and on overall risks and benefits in predominantly healthy women."*

RCT :16,608 women 50-79yo on Premarin .625mgs and Provera 2.5mgs(Prempro) vs placebo. Study halted at 5.2 years, 3 years early.:

Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial.
Rossouw JE, JAMA. 2002 Jul 17;288(3):321-33.

Women's Health Initiative Study:

- 8/10,000 more women/year would develop Breast CA
- 7/10,000 more women/year would have a MI
- 8/10,000 more women/year would have a CVA
- 6/10,000 fewer women/year would develop colorectal cancer
- 5/10,000 fewer women/year would suffer a hip fracture

Women's Health Initiative Study:

- "Results from WHI indicate that the combined postmenopausal hormones CEE, 0.625 mg/d, plus MPA, 2.5 mg/d, should not be initiated or continued for the primary prevention of CHD."
- "This trial did not address the short-term risks and benefits of hormones given for the treatment of menopausal symptoms."

Women's Health Initiative Study

"The results do not necessarily apply to lower dosages of these drugs, to other formulations of oral estrogens and progestins, or to estrogens and progestins administered through the transdermal route. It remains possible that transdermal estradiol with progesterone, which more closely mimics the normal physiology and metabolism of endogenous sex hormones, may provide a different risk-benefit profile."

CEE-Alone Component of the (WHI)

RCT *disease prevention trial* 10 739 , 50-79 y.o. postmenopausal women, with prior hysterectomy.

CEE increases risk of CVA, decreases risk of hip fracture, and does not affect CHD incidence and possible reduction of breast cancer in over an average of 6.8 years.

Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. Anderson GL, et.al. JAMA. 2004 Apr 14;291(14):1701-12.

CEE-Alone Component of the (WHI)

The burden of incident disease events was equivalent in the CEE and placebo groups, indicating no overall benefit.

CEE should not be recommended for chronic disease prevention in postmenopausal women.

"Overall, these data support the current US Food and Drug Administration recommendations for postmenopausal women to use CEE only for menopausal symptoms at the smallest effective dose for the shortest possible time."

E3N-EPIC Cohort Study

Risk of breast cancer associated with HRT use in 54,548 postmenopausal women who had never taken any HRT 1 year before entering study. (Mean HRT use was 2.8yrs.)

- Estrogens used alone the RR was 1.1
- HRT containing synthetic progestins the RRs was 1.4.
- HRT containing micronized progesterone RR was 0.9.

"Our results suggest that, when combined with synthetic progestins, even short-term use of estrogens may increase breast cancer risk."

Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. Fournier A, Int J Cancer. 2005 Apr 10;114(3):448-54.

ESTHER Study

- Multicenter case-control study of VTE among postmenopausal women 45 to 70 years of age.
- 271 with VTE and 610 matched controls.
- Odds ratio of VTE in current users:
  - Oral Estradiol (E2): 3.5
  - Transdermal E2: 0.9

"CONCLUSIONS**:** Oral but not transdermal estrogen is associated with an increased VTE risk."

Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. Canonico M, Circulation. 2007 Feb 20;115(7):840-5.

Estrogen and VTE

- Meta-analysis of observational studies
  - Caronica et al 2008 BMJ 336(7)1227-31
- Odds ratio
  - Oral E2 2.5 (Highest in first year of use)
  - Transdermal E2 1.2
- Concluded oral estrogen increases prothrombin 1+2 fragment, a marker of in vivo thrombin generation, via the 'first pass' effect on the liver.

Estrogen and Heart Disease

- WHI:
  - CEE/MPA RR=1.29
  - CEE RR 0.91
- Oral Estrogen reduced heart disease
  - In line with many previous studies
- This effect COMPLETELY negated with daily use of MPA
  - Works at endothelial level to block estrogen induced increases in nitric oxide and alters endothelial function.

There is a wealth of evidence to suggest that, unlike oral estrogens, transdermal estradiol does not increase the risk of venous thromboembolism, probably due to its lack of effect on the coagulation cascade, including thrombin generation and resistance to activated protein C, and does not increase the risk of stroke. It is cardioprotective, significantly reducing the incidence of myocardial infarction compared with non-users; it significantly reduces the incidence of new-onset diabetes, a risk factor for myocardial infarction. Micronized progesterone has also been shown not to increase the risk of venous thromboembolism and further reduced the incidence of new-onset diabetes when combined with transdermal estrogen. Micronized progesterone has a neutral effect on the vasculature, including a neutral or beneficial effect on blood pressure. Therefore, experimental and clinical data indicate that transdermal estradiol and micronized progesterone could represent the optimal HRT, particularly in women at risk of adverse events.

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

Estrogen and Progesterone Possible Side Effects and Risks:

- Irregular vaginal bleeding
- Thickened uterine lining
- Weight gain
- Breast and nipple tenderness
- Possible increase risk of breast cancer?
- In older women beginning >60yo beginning HRT may increase risk of CAD/CVA?

Contraindications to Estrogen and Progesterone Therapy:

- Hormone sensitive breast cancers
- Ovarian cancer
- Metastatic uterine cancer
- Endometriosis

Male Climacteric/ Andropause:

- Beginning of diminishing virility but not necessarily fertility.
- Decreasing secretion of GnRH and testicular response to FSH and LH resulting in lower testosterone production.
- SHBG increases resulting in lower free testosterone.

Andropause/ Low "T" Symptoms

- Decreased Libido
- Erectile dysfunction
- Difficulty achieving orgasm/ decreased intensity
- Low energy/fatigue
- Loss of motivation
- Irritability
- Accumulation of fat
- **Loss of muscle mass and strength**

Serum Testing

- Testosterone, Free Testosterone
- PSA
- FSH, LH, Estradiol, SHBG, ?DHT
- TSH, fT4, fT3, rT3, thyroid antibodies
- DHEAS
- Cortisol a.m., p.m.
- Vitamin D
- CBC, ferritin, Vitamin B12
- LFTs, Cholesterol, CRP, ANA, RF

Low T and ?Pain?

- No direct causality between low T and pain
- Low testosterone increases the risk of osteoporosis and fractures from falls in men.
- Decreased muscle mass may lead to increased injuries.

Testosterone Therapy

- Andriol – oral pharmaceutical testosterone. Increase risk of Liver disease and Cholesterol abnormalities.
- Androgel – topical pharmaceutical Testosterone 50, 75 or 100mgs of testosterone in alcohol based gel.
- Compounded testosterone cream 25-300 mgs.
- Testoterone cypionate IM – 50-200mgs/week.

Possible Side Effects and Risks

- Decreases HDL.
- Increases clotting factors.
- Increases Hemoglobin production.
- Increased PSA and prostate volume.
- May decrease testicular size and decrease sperm production.

Testosterone Therapy & Prostate Cancer

Systemic Review: none of the studies demonstrated that testosterone therapy increased prostate cancer risk or increased Gleason grade of cancer detected in treated vs untreated men.

Shabsigh R, Testosterone therapy in hypogonadal men and potential prostate cancer risk: a systematic review. *Int J Impot Res. 2009 Jan-Feb;21(1):9-23*

Testosterone Therapy & Heart Disease

Meta-Analysis: There is no convincing evidence of increased CV risks with T therapy. On the contrary, there appears to be a strong beneficial relationship between normal T and CV health that has not yet been widely appreciated.

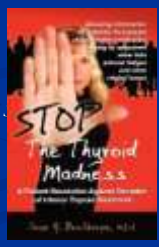
Morgentaler A, Testosterone therapy and cardiovascular risk: advances and controversies. Mayo Clin Proc. 2015 Feb;90(2):224-51.

Contraindications for Testosterone Therapy

- Breast or prostate cancer
- Palpable prostate nodule or swelling
- PSA greater than 4
- Hematocrit greater than 50%
- Untreated severe obstructive sleep apnea
- Severe lower urinary tract symptoms
- Uncontrolled or poorly controlled heart failure.

Musings on Thyroid Hormone and Pain

- Optimal levels of TSH - .35-1.5/2
- fT3 and reverse T3
- T4 vs Desiccated Thyroid hormone
- Muscle and Joint Pain



Wartofsky LJ, The evidence for a narrower thyrotropin reference range is compelling.Clin Endocrinol Metab. 2005 .

Nygaard B, Effect of combination therapy with T4 & T3 versus T4 monotherapy in patients with hypothyroidism, a double-blind, randomised cross-over study. Eur J Endocrinol. 2009

Patient Case Surgical Menopause

- 48yo woman 3 years post oophorectomy for BRAC2 gene. Breasts intact.
- c/o hot flashes, sleep disturbance, irritability, vaginal dryness, weight gain, poor energy and loss of libido.
- TSH 2.85, free and total testosterone <.5, DHEAS 2.9.
- Biest E2 0.75mgs, E3 .15mgs/Testosterone 3mgs, Progesterone 100mgs qhs, DHEA 10mgs, Thyroid hormone 60mgs.
- 4 months after 'tweaking' hormone levels, "You've given me my life back!!"
- Husband called to book appointment for himself.

Patient Case 1 – 52 y.o. woman LMP>1 year ago

"Feeling terrible" especially last 6 months. Hot flashes, sleep disturbance. Vaginal dryness, low libido. "it hurts". Dry skin, eyes and hair. Itchy skin. Irritable and weepy. Very achy and stiff. Joints hurt.

Rx'd Transvaginal Biest E2 0.75mgs/E3 0.15mgs daily; Progesterone 100mgs qhs.

F/U in 4 weeks. Requisition for blood work given.

Patient Case 1 – 52 y.o. woman LMP>1 year ago

4 weeks later: Hot flashes almost gone! Sleeping. Vaginal dryness also gone. Libido, mood and energy much improved. Skin, hair, eyes might be a bit better. Aches and pains improved by about 25%

- sTSH- 1.51; T4 – 15; T3 – 5.2; Testosterone – .6; Free Testosterone 12.; DHEAS – 4.9.

Repeat Rx. F/U in 8 weeks.

Next appointment. Hot flashes, pain and stiffness are gone. Hair eyes and skin are much improved. "I feel like my old self again."

Patient Case 2 – 64 y.o. man with fatigue

Retired a few years ago. Fatigues easily after 1-2 hours of activity. Libido is poor. Saw family doctor. Told him that he's getting older. Also has a shoulder injury.

Testosterone -9.2 ; Free Testosterone -17; DHEAS -6.5; TSH -1.25; fT4 17; fT3 - 4.7.PSA, CBC, LH, FSH, Prolactin are in normal range.

Rx Testosterone gel 100mgs/dose. 1 dose daily.

Patient Case 2 – 64 y.o. man with fatigue

- F/U in 6 weeks – Energy has improved, able to accomplish more at home. Mood is better, feels more positive. Libido has improved as well. Notices that shoulder is less painful!
- Testosterone -20 ; Free Testosterone -42; PSA no change.
- Repeat Rx.
- F/U in 8 weeks. Continues to feel well. Shoulder has healed!

Patient Case 3 – 52 y.o. man with weight gain.

- Over the years has put on 35lbs. Easy to put on hard to take off. Libido is good. Energy pretty good but not like it used to be.
- TSH – 3.88; fT4 – 17; fT3 – 4.2 Remainder of hormone panel normal.
- Rx'd thyroid hormone 90mgs.

Patient Case 3 – 52 y.o. man with weight gain.

- F/U 8 wks –Better energy and able to work out more efficiently. Realized that he was achy. Thought that it just came with age. All aches and pains are gone! Lost 5lbs.
- TSH – 1.2; fT4 – 16, fT3 – 5.0

Questions?