Bioidentical Hormones: What’s true, What’s not

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Between Natural and Conventional Medicine
OVERVIEW

- A brief history
- A clinician’s dilemma
- What evidence exists
- What we don’t know
- Sorting through hype, hope and scant data
- Applying common sense toward safe and reasonable use of natural hormones
Learning Objectives
Participant will:
1. receive an overview of the history of use of natural or "bioidentical" hormones in menopause as well as some of the issues with oversight, regulation, popular promotion and research of compounded and OTC products available to patients in the U.S.
2. become familiar with issues regarding safety, indications, contra-indications, dosing and forms of natural estrogens and progesterone marketed as "bioidentical".
3. begin to sort through the claims of both proponents and the concerns of opponents of natural hormone use in applying evidence and physiology toward safe and effective prescribing.

DISCLOSURE:
Is there anything to disclose? Yes
Please list the Potential Conflict of Interest (if applicable): Theoretical: I authored a book on Menopause which could potentially get mentioned in my introduction or content.

All Potential Conflicts of Interest have been resolved prior to the start of this program.
Yes (If no, credit will not be awarded for this activity.)

COMMERCIAL SUPPORT ORGANIZATIONS: None
DEFINITIONS

- “Bioidentical”-molecularly identical to that produced in the human body
- “Natural hormones” = “bioidentical hormones”
- E1-Estrone  E2-Estradiol  E3-Estriol
- MP-micronized (natural) progesterone
- BHRT = bioidentical hormone replacement
TOPICS

- Compounded and FDA approved natural hormones
  - Estriol, Estradiol,”Tri-est” & “Bi-est”, micronized progesterone (oral, transdermal, vaginal applications)
    - Endometrial protection
    - Cardiovascular implications
    - Breast cancer risk
    - Effect on bone
    - Reasonable vs. dubious indications

- Hormone testing, compounding pharmacies
QuickTime™ and a decompressor are needed to see this picture.
A brief history of “bioidentical” hormones

- **1975** FDA Approves Estrace®

- **1978** JAMA “Estriol, the forgotten estrogen?”
  - Urges doctors to use E3 rather than E2

- **1980s-present**: small estriol (E3) studies (Japan, Europe)
A brief history of “bioidentical” hormones

- **1983** Jonathan Wright MD introduces “Natural Hormones” as a specific approach

- **Tri-est** (1:1:8 = E1:E2:E3)
  - Common dose: 1.25 mg bid
  - = 1mg Estriol, 0.125 mg each of estradiol and estrone

- **Bi-est** (1:4 = E2:E3)
  - Common dose: 1.25 mg bid
  - = 1mg Estriol, 0.25 mg each of estradiol and estrone

- uses DHEA clinically
A brief history of “bioidentical” hormones

- **1980-present**: Micronized progesterone used widely in Europe

- **Dosages**:
  - 300 mg/day 10 days/mo
  - 200 mg/day 14 days/mo
  - 100 mg 25 days/mo

A brief history of “bioidentical” hormones

- **1990** John Lee MD
  - Claims for natural progesterone:
    - builds bone
    - decreased vasomotor symptoms
    - improved libido
    - decreased breast cancer risk, improved PMS, fibrocystic breast, endometriosis…
  - Coined “estrogen dominance”
  - Salivary hormone testing
A brief history of "bioidentical" hormones

1990-2002

Licensed practitioners of natural medicine (MD, ND, DO, NP, PA) Rxed compounded BHRT products
- Tri-est
- Bi-est
- Testosterone
- DHEA

OTC natural progesterone creams
A brief history of “bioidentical” hormones

FDA Approved
Standardized 17b-Estradiol products

- **Oral:** Estradiol (generic), Estrace *(1975)*
- **Patches:** (Estraderm, Alora, Vivelle, Vivelle dot, Climara, Esclim, Menostar)
- **Creams:** Estrace, Estrogel, Elestrin, Divigel
- **Topical emulsion:** Estrasorb *(2004)*
- **Transdermal spray:** Evamist *(2007)*
- **Vaginal Ring:** Estring, Femring *(2003)*
A brief history of "bioidentical" hormones

- **1998** FDA approves Prometrium
  - Use with CEE in non-hysterectomized women
    - 200 mg 12 days/mo
  - Secondary amenorrhea
    - 400 mg x 10 days

- Commonly used dosing regimens:
  - Continuous: 100-200mg QD or 25 days/mo
  - Cyclical: 200-400mg 10 days/mo
A brief history of “bioidentical” hormones

- **Oct 6, 2005**, Wyeth--citizen action petition with FDA requesting they take action against compounding pharmacies which make bio-identicals.

- **Jan 9, 2008** FDA action
  - warnings issued to seven individual compounding pharmacies
  - press conference for the public about BHRT.
  - Their main objections:
    - Estriol
    - the term “bio-identical”
    - lack of scientific evidence
A clinician’s dilemma
Dr. L. Schoenbeck:

Re:

Enclosed Please find the Saliva Test Results for  

Dated 12-03-09

Chief Complaints: Hot Flashes; Night Sweats;  
Foggy Thinking; Memory Lapses;  
Sleep Disturbed: Morning & Evening Fatigue  
Symptoms of Adrenal Fatigue - Excess Stress;  
General Symptoms of Progesterone: Estradiol Deficiency

Saliva Test Results: - Progesterone is In-Range; But Estradiol is High-Range;  
- Low Ratio: Progesterone/Estradiol  
- Normal Testosterone & DHEAS;  
- Cortisol is High-Range - Symptoms of Stress & Adrenal Fatigue are Prevalent;

I can help Ms. ............... with her Cortisol problem with the use of Education, Targeted Supplements and Dietary & Life-style Changes. This should also help Reduce her High-Range Estradiol Level as well.

To Help with this, it is imperative that we get the Ratio of Estradiol: Progesterone be brought into Balance.

This can be done by the addition of a Compounded Progesterone Topical Cream to the above Regimen.

If you have no objections, please authorize the following Prescription:

Progesterone Topical Cream 20% ................. 30gm  
To be applied once daily Monday to Saturday - Off Sunday  
Refill x 11

If you have any questions, please feel free to contact me by phone or email at your convenience.

Thank you, I remain...
Hormone Evaluation

2009 12 03 090 S

Samples Arrived: 12/03/2009
Date Closed: 12/04/2009

Gender: Female
Client Phone: 802-528-4330
Age: 54

Menopausal Status: Postmenopausal

Hormone Test | In Range | Units | Out Of Range | Range |
---|---|---|---|---|
Testosterone (total) | 41 | pg/ml | 24H | 0.5-17 | Postmenopausal (optimal 1.3-17) |
Progesterone (total) | 17L | pg/ml | Optimal: 100-500 where E2 1.3-3.3 pg/ml |
Testosterone (total) | 33 | ng/ml | 16-65 (Age Dependent) |
DHEAS (total) | 8.0 | ng/ml | 2.25 (Age Dependent) |
Cortisol Morning (total) | 11.9L | | 3.7-6.5 |

Current Hormone Therapies
None.

David T. Zava, Ph.D.
Laboratory Director

Date: 12/04/2009
CLIA Lic #: 38D0960930

This lab's results and comments are for informational purposes only and are not to be construed as medical advice. Please consult your healthcare provider for diagnosis and treatment.
Salivary E/P hormonal testing

*Proposed* rationale (John Lee MD)
- Progesterone lipophilic, transported by RBC membranes
- Plasma/serum levels detect protein-bound progesterone and not “free” or tissue-available progesterone
- Salivary levels more closely reflect tissue availability

*The Problems*
- Correlation to clinical symptoms??
- Premenopausal E/P levels change every day
Menopausal “hormonal testing” of any kind

---> Bottom line: rarely helpful

Possible exceptions:
- FSH in non-oophorectomized hysterectomy patients in assessing cause of symptoms
- Androgens: Testosterone, DHEA(s)
- Bone protection (E2>40pg/mL) (newer data >10 pg/mL) (Speroff and Fritz, Clinical Gynecologic Endocrinology and Infertility)
What do we know about E3? (Estriol) ("The weaker estrogen")
Estriol (E3)

- Weak metabolite of E1 & E2
  - Some potentially metabolized directly from androstenedione
- 1-2% orally administered estriol (E3) enters bloodstream. Peak levels achieved in 3-4 hrs.
- A fatty meal 4 hrs p oral administration results in another spike: entero-hepatic recirculation.
Vaginal (compared with oral) administration has been shown to result in 10x serum levels of E3 as compared to oral. Meals have negligible effects.

E2 agonist-antagonist. Competitive binding to ER. Factors affecting this:
- Estradiol and estrone concentrations
- Temperature

Binds more weakly to SHBG than E2
Estriol (E3)

- 150 Postmenopausal women
- 1 mg E3 x 2 years

Kupperman Menopausal Index
- Vasomotor instability (hot flushing)
- Insomnia
- Headache
- Excessive sweating
- Depression
- Nervousness, dizziness, jt pain, tremor, tachycardia, irritability, lack of concentration

Ave. score: 34 pretx, 20, 10, 6 (months 1,2,3)

Estriol (E3)

- 68 postmenopausal women
- 2 mg oral estriol x 12 months
  - Menopausal (symptom) Index improved significantly, esp. vasomotor symptoms
  - 5 women had self-limiting vag. spotting for 2-3d
  - EMB showed atrophic endom. in most of the women at 12 months, weakly proliferative endom. in 17.6%, no atypical hyperplasia
  - No change in lipids or bone markers
- 93% women wanted to continue the therapy

Efficacy and safety of oral estriol for managing postmenopausal symptoms K. Takahashi et al. Maturitas 2000 (34)164-177
Estriol and atrophic vaginitis

- Beth Israel Deaconess Medical Center, Boston
- 19 postmenopausal women with atrophic vaginitis
- Vaginal suppositories 1 mg estriol plus 30 mg progesterone nightly x 2 weeks, then 3x/week x 6 mo
  - EMB at baseline and 6 months
  - Vaginal Maturation Index, vaginal pH, vaginal dryness rating improved significantly
  - Menopause QOL scores improved, most in sexual subscale
- No endometrial hyperplasia
  - Menopause 2009 Sept-Oct;16(5)978-83
Estriol for recurrent UTIs in postmenopausal women

- 93 postmenopausal women with recurrent UTIs (RCT)
- Randomized to 0.5 mg E3 or placebo cream, (x 2 weeks, then 2x/wk for 8 mo)
- RESULTS: 0.5 UTIs / pt yr in E3 group
- 5.9 UTIs / pt yr placebo grp
- Lactobacilli appeared 61% E3 grp, 0% placebo grp

Estriol and breast cancer

- E3 reversed breast cancer in animal models

- E3 given to women with breast cancer for menopausal symptoms resulted in 37% of women experiencing remission

- In vitro study: E3, like E1 and E2, activated breast cancer cells. Addition of Tamoxifen did not prevent this activation
Estriol and cardiovascular disease

Women’s Integrative Medicine Department, Southwest College of Naturopathic Medicine, Tempe, Arizona

“Based on the current evidence, the same cardiovascular risks that have recently been found to be associated with oral HRT may also be associated with the administration of oral estriol in BHRT.”

Estriol and bone

Intervention: 1g Calcium vs. 1g Ca + 2 mg Estriol x 10 mo.

- 20 postmenopausal women (50-65)
  - 18 completed study
- 29 Elderly women (70-84)
  - 23 completed (vag bleeding most common S.E.)

RESULTS:
- Postmenopausal treatment group BMD +5.59% ave. vs. -4.02 in Ca only group
- Elderly treatment group BMD + 3.32% ave. vs. -3.26% Ca only group. -Journ Bone and Mineral Metab, March 1998
Estriol summary

- Most likely effective as local treatment for vaginal atrophy and recurrent cystitis related to hypoestrogenism.
- Assume same risks as E2--data insufficient to assert otherwise. C/I in women with hx. breast cancer or atypical breast hyperplasia.
- Same cardiovascular risks as conventional ERT.
- Not likely to prevent or treat osteoporosis.
- Oral or vaginally-administered doses achieving systemic effects need progesterone to prevent endometrial hyperplasia.
Oral micronized progesterone

- 90% metabolized on first pass; absolute bioavailability 6-8% (similar to estradiol)
- Metabolites:
  - pregnanediol, pregnenolone, pregnanedione, 20a-dihydroprogesterone, 17-OH-progesterone
- Potential side effects: dizziness, fatigue, depression, bloating, wt gain, GI complaints.
  - Medroxyprogesterone acetate (MPA) and norethindrone acetate have been designed to resist this metabolic degradation, but are fraught with some of these same side effects.
Progesterone vs. MPA

  - 875 menopausal women, double-blind, randomized, placebo controlled trial x 3 yrs
  - 5 groups
    - Placebo, CEE alone, CEE + continuous MPA 2.5mg, CEE + cyclic MPA, CEE + cyclic Micronized Progesterone
  - Outcome comparing MPA and MP:
    - fewer episodes of excessive bleeding
    - Equally effective in preventing endometrial hyperplasia
    - HDLs 3.5 fold increase in the group using MP than in those receiving MPA.
Micronized progesterone

- **Side effect profile vs. MPA**

- Decreased fluid retention, breast tenderness, depression, weight gain

- QOL improved, less break-through bleeding “significant improvement in vasomotor symptoms, somatic complaints, and anxiety and depressive symptoms” when compared with MPA (Mayo study 176 women)
Progesterone and thromboembolic events

- **ESTHER Study**
  - French multicenter case control study of VTE among postmenopausal women 45 to 70 years of age between 1999 and 2005 in France. 271 consecutive cases with a first documented episode of idiopathic VTE and 610 controls

- Compared thromboembolic events in women on different progestin/progesterone regimes

- **RESULTS:**
  - Odds ratio of micronized progesterone with Venous Thromboembolism vs. controls 1:1
  - With Medroxyprogesterone acetate (MPA) 1:3.8
Progesterone and breast cancer

- Synthetic progestins found to further increase breast cancer risk beyond estrogen use
  - **WHI** [RR] 1.26 among CEE + MPA users vs. controls.
    - No clear increase among CEE only users.
  - **Nurse's Health Study** (followed 58,000 postmenopausal women for 15 years, late 1990s):
    - Ages 50-60 addition of progestin to ERT--67% inc. risk, vs. 23% inc risk from estrogen therapy alone
Progesterone and breast cancer

- **E3N Cohort Study** (France) 80,377 postmenopausal women for 8.1 years. (1990-2002 French component of European study into Cancer and Nutrition.)

  In France ERT=E2
  
  - [RR] 1.29 with ERT alone,
  - [RR] 1.69 ERT with progestin
  - [RR] 1.00 ERT with MP
- No HRT
  - E2 alone Ave. [RR] 1.29
    - E2 alone <2 yrs use
    - 2-4 yrs
    - 4-6 yrs
    - 6+
  - E2 + Progesterone Ave [RR] 1.0
    - <2 yrs
    - 2-4
    - 4-6
    - 6+
  - E2 + Dydrogesterone [RR]1.16
    - <2 yrs
    - 2-4
    - 4-6
    - 6+
  - E2 + MPA Ave. [RR] 1.69
    - <2 yrs
    - 2-4
    - 4-6
    - 6+
  - Weak estrogens
  - unknown HRT
  - mixed
Oral micronized progesterone: (OMP) summary

- Protects the uterus from hyperplastic changes associated with estrogen-only therapy.
- FDA approved for HRT at 200 mg 14 days/mo. (Prometrium®) Also likely effective at 100 mg =>25 days/mo.
- Is preferred to progestin regarding its cardiovascular profile
- Is generally well-tolerated compared to progestin.
- May offer less breast cancer risk than progestin. More study needed.
Transdermal progesterone “i.e. progesterone creams”

Assessing menopausal sx, lipid, bone response

- 80 postmenopausal women, randomized, double-blind trial-32 mg progesterone cream vs. placebo x 12 weeks
- Assessed for symptoms, bone markers and lipids
- RESULT: No change in vasomotor symptoms, mood characteristics, or sexual feelings, blood lipid levels or in bone metabolic markers, despite a slight elevation of blood progesterone levels

Menopause: January 2003 - Volume 10 - Issue 1 - pp 13-18 Wren et al. Transdermal progesterone and its effect on vasomotor symptoms, blood lipid levels, bone metabolic markers, moods, and quality of life for postmenopausal women
Transdermal progesterone and the endometrium


- 26 postmenopausal women x 6 months-0.625 mg CEE + 2.5 mg MPA vs. 0.625 mg CEE + 20 mg progesterone cream bid

- 52 post-treatment biopsies:
  - 40 atrophic endometrium
  - 12 proliferative endometrium (7 on oral progestin/ 5 on progesterone cream)
  - No evidence of endometrial hyperplasia in either group

Similar vaginal spotting between groups
Transdermal progesterone and the endometrium

- 27 postmenopausal women over 3 cycles
- continuous transdermal estradiol plus cyclic transdermal progesterone cream days 15-28-doses of progesterone 16, 32 or 64 mg taken sequentially
- blood, saliva and endometrial samples taken

RESULT:
- Physiological doses of estradiol and endometrial proliferation achieved
- No correlation between doses of progesterone and biological activity
- No secretory changes in the endometrium achieved
- One patient experienced bleeding
  - Climacteric. 2000 Sep;3(3):155-60
Transdermal progesterone and the endometrium

- 54 postmenopausal women x 48 wks
- 1 mg transdermal E2 + 40 mg transdermal progesterone
- 32% evidence of inadequate endometrial protection
  - Baseline end. Thickness 3.3mm ave.
  - 5.3 mm at 24 wks; 5.5 mm at 48 wks
  - 27% end. proliferation; 5% complex (1 woman with atypia)
Transdermal progesterone “i.e. progesterone creams”

CONCLUSION:

- Current evidence does not support the use of progesterone creams as adequate endometrial protection w/ ERT.

- Reasonable clinical uses: Premenopausal women not on ERT
  - PMS
  - Dysmenorrhea
  - Menorrhagia

--Potential side effects same as OMP
Testosterone

- No FDA approved HRT product available
- Compounding products available
  - Lozenges, oral capsules, creams
- Most consistent blood levels: Cream
  - 1-5mg/day.
  - Testing mandatory before and after Tx.
  - Adverse effects: acne, hirsuitism, aggressive behavior, cholesterol elevation (very rare: clitoral enlargement, vocal changes)
Compounding pharmacies

- Traditional compounding:
  - Tailoring to the needs of an individual patient
  - Dosages not conventionally available
  - Preparations removing allergens
  - Flexibility of administration methods
Compounding pharmacies

- regulation of compounding pharmacies via state pharmacy boards
  - Other Gov. bodies regulating compounding pharmacies: USP, DEA, OSHA, EPA
- not under FDA (federal) jurisdiction
  - FDA oversees manufacturers and suppliers
- USP requirement of drug
  - +/- 5 % labeled amount
Compounding pharmacies

Hormone raw material sources:

- Soy, wild yam, synthetic
- Same for FDA approved and compounding pharmacy versions of BHRT
- Distributors: Diosynth, Gedeon Richter, Pfizer, Syntex, Proquima...
BHRT Summary

- **BHRT is HRT.** Careful risk/benefit assessment by qualified provider essential
  - More study needed before we will know estriol’s effect on breast cancer risk. C/I in women w/ breast cancer or CVD
  - Oral MP preferable to progestin in HRT. Transdermal MP not proven effective ERT opposition.
  - Vaginal estriol preparations may be effective in atrophic vaginitis and recurrent UTIs
  - Many FDA-approved BHRT options exist
  - Local compounding pharmacies offer options for individually-tailored dosing and forms when an appropriate conventional medication is not available
  - Salivary E/P hormone testing not recommended