Hormone Replacement Therapy

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HRT

- No financial or conflict of interest disclosures

Objectives

- Practical guide to HRT
- Bioidenticals – evidence, review common misconceptions
- Review alternatives
- Special cases – perimenopause, cancer,

Case study

- Compounded Bioidentical Menopausal Hormone Therapy
- Fertility and Sterility® Vol. 98, No. 2, August 2012 0015-0282

Quick facts of menopause

- Def'n : Retrospective diagnosis. One year of ammenorhea
- Avg age of menopause 51
- Avg length of symptoms is 7 years
- Improvement of these symptoms after the first two years
- Number one presenting symptom to office - hot flashes

Questions

TIMING – Should I start? When to start? when to stop?

AGENT – Which estrogen/progesterone?what dose? What mode?

ALTERNATIVES – Do they work?

BIOIDENTICALS – Evidence for them. How do they fit in?

VAGINAL ESTROGEN – How long? What if cancer?

SPECIAL CASES – Perimenopause, cancer, cognition

TIMING

Know your patient

- Obesity
- Diabetes
- Hypercholesterolemia
- Breast Ca family hx
- Cardiac hx
- DVT in the past
- HTN
- EtOH and smoking Hx

WHI 2002 and beyond…

- E&P – 16000 women stopped after 5 years

Increased risk of CHD and Breast CA

- CEE – 10000 women stopped after 7 years

- 60% of women were greater then 60 years old
- Generalized findings to a group that was not well represented .. The 50-59 y.o just entering menopause

NAMS and IMS

- There is less risk for the age group 50- 59

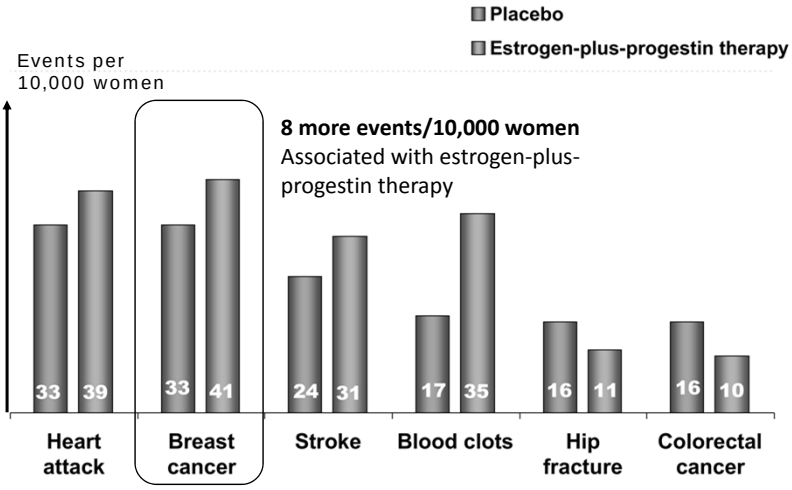
Estrogen plus progestin resulted in:

- Increased risk of heart attack
- Increased risk of stroke
- Increased risk of blood clots
- Increased risk of breast cancer
- Reduced risk of colorectal cancer
- Fewer fractures
- No protection against mild cognitive impairment and increased risk of dementia (study included only women 65 years and older)

Estrogen alone resulted in:

- No difference in risk for heart attack
- Increased risk of stroke
- Increased risk of blood clots
- Uncertain effect for breast cancer
- No difference in risk for colorectal cancer
- Reduced risk of fracture

Assessing the Results of the WHI Estrogen-Plus-Progestin Study



Writing Group for the Women`s Health Initiative Investigators. JAMA, 288 (3), 321-333, 2002

The Estrogen Replacement Therapy arm of the WHI Study, which includes over 10,000 hysterectomized women, is scheduled to continue until March 2005.[1]

The chart below, showing the clinical outcomes from the WHI Study, outlines the increase/decrease in health events per 10,000 women annually for those not taking HRT (placebo) vs. those taking combination HRT.[1*]

Outcomes	Outcomes/ 10,000 women/year taking placebo	Outcomes/ 10,000 women/year taking combined HRT	Relative risk vs. placebo (Hazard ratio [nominal 95% CI†])	Absolute difference/ 10,000 women/year
Invasive Breast Cancer	30	38	26% (1.26 [1.00-1.59])	8 more women with breast cancer
Coronary Heart Disease	30	37	29% (1.29 [1.02-1.63])	7 more women with heart attacks
Stroke	21	29	41% (1.41 [1.07-1.85])	8 more women with strokes
Blood Clots (Thromboembolic Events)	16	34	111% (2.11 [1.58-2.82])	18 more women with blood clots
Hip Fracture	15	10	-34% (0.66 [0.45-0.98])	5 fewer women with hip fractures
Colorectal Cancer	16	10	-37% (0.63 [0.43-0.92])	6 fewer women with colorectal cancer

NEW SOGC 2014 UPDATE:

Vasomotor symptoms:

1. Health Care Providers should offer HT (E alone or EPT) as the most effective therapy for menopausal Sx.
2. P. Alone or low dose ocp can be offered during transition
3. Early menopause or POF or surgical menopause should be offered HRT until normal age (51) of menopause
4. BOTTOM LINE: lowest dose, shortest time, full disclosure of risks!

Take Home messages

- Maybe less risk then we thought for 50- 59 group then the WHI study implied
- More thinking that E&P together is the culprit for causing cancer.
- Counsel your patient taking into account the statistics, but also considering their individual risks

BOTTOM LINE

- BOTTOM LINE: lowest dose, shortest time, full disclosure of risks!
- Less risk if start within the first two years of menopause. (50-59 age category)

"It's always best to start with a low dose and closely monitor the results."

AGENT: What to use?

- Which is estrogen?
- Which progesterone?
- What dose?
- How long?

Lowest dose to treat symptoms

- Pt's are their own biological assay
- Treat to alleviate symptoms
- Serum blood tests don't correlate with presenting symptoms or symptom alleviation

Pt's record symptoms for 3/12 then follow up

Reassess every year

Tips for route of delivery

- Pt. preference and adherence
- What symptoms are bothering them the most (ie vaginal atrophy?)
- Efficacy – Transdermal better for smokers
- Cardiovascular impact – Decreased VTE with transdermal

.

Progesterone

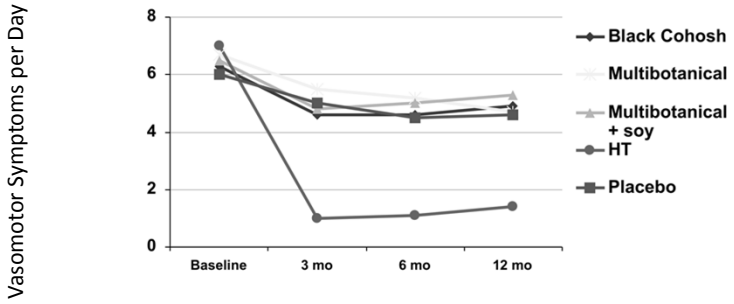
- Need minimum of 12 days of progesterone for protection
- If don't want to cycle then do a combo of E&P
- Give 3-4 months to settle, may have some spotting.
- If still bleeding will need an endometrial biopsy

DUB

- Anyone over 40 who has a significant change in their bleeding (heavier, more frequent, seeking care for this)
- Anyone greater then a year with no menses and starts bleeding.
- NEEDS ENDOMETRIAL BIOPSY

ALTERNATIVES

Vasomotor Symptoms:
Herbals and Botanicals No Better Than Placebo



*Multibotanical delivered daily doses of the following:
black cohosh 200 mg; alfalfa 400 mg; boron 4 mg; chaste tree 200 mg; dong quai 400 mg; false unicorn 200 mg; licorice 200 mg; oats 400 mg; pomegranate 400 mg; iberian ginseng 400 mg

Newton KM et al Ann Intern Med 2006;145: 869-879

Any other options?

Non-Hormonal Prescription Therapies

Antidepressant	Effexor: 37.5-75 mg/d
Anticonvulsant	Gabapentin: 300-900 mg/d
Antihypertensive	Clonidine*: 0.05 mg twice daily

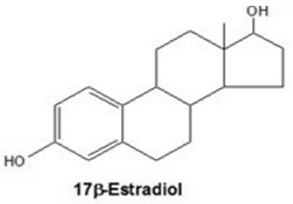
* Only non-hormonal medication approved in Canada for the treatment of vasomotor symptoms

SOGC clinical practise guidelines 2006

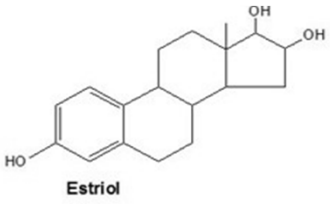
BIOIDENTICAL HORMONES:

Refers to the structure
NOT
the source of the hormone

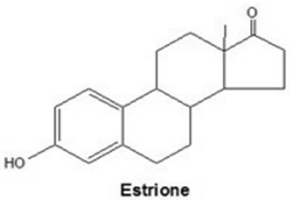
The 3 estrogens produced by our bodies:



17β-Estradiol



Estriol



Estrione

Common myths

- Bioidentical is synonymous with natural
- If it's natural it's safe
- They are more effective
- If it's from a pharmaceutical company it can't be bioidentical

SALIVA TESTING

- THEORY:
- Blood ultrafiltrate
- Saliva concentration should correlate with free/unbound serum concentration

- REALITY
- Correlations vary:
- Time of day
- Diet
- Specific hormone tested
- Poor reproducibility
- Large interassay variability
- Large within pt. variability

Boothby, Menopause 2004;11:356-367

INDIVIDUALIZED DOSING:

Need a predictable relationship between dose and therapeutic response

WE do not have that with hormones

BOTTOM LINE: hormone dosing is completely based on empirical starting point and adjusting based on symptomatic relief (hot flushes) or another clinical end point (bone density)

BIOIDENTICAL PROGESTINS

Diosgenin- from yams

PROGEST= 200 mg progesterone/ounce
Typical dose = ½ -1 tsp on skin (very low absorption)

Study- prometrium oral 9.5nmol/L vs. Progest 2.9nmol/L
Progest DOES NOT protect the endometrium
Salivary levels showed an increase with Progest BUT NOT blood levels!

FDA APPROVED: BIOIDENTICAL ESTROGENS

Anything produced by a YAM or a SOYBEAN
Is in fact BIOIDENTICAL

FDA approved bioidenticals:
Estrace/Ogen
Climara/Estalis/Estracomb/Estradot/Estraderm
Estrogel

FDA APPROVED: BIOIDENTICAL PROGESTINS

PROMETRIUM IS BIOIDENTICAL

Safety vaginal estrogen

Ulrich et al 2010

•no evidence of increased endometrial thickness after 1 year of treatment

Simon et al 2010

•two events of hyperplasia and carcinoma were reported in 386 endometrial biopsy samples (incidence rate 0.52% per year)

•incidence of endometrial hyperplasia and carcinoma in menopausal women is < 1%

Simon J, Nachtigall L, Ulrich LG, Eugster-Hausmann M, Gut R. Endometrial safety of ultra-low-dose estradiol vaginal tablets. Obstet Gynecol. 2010;116(4):876–883.
Ulrich LS, Naessen T, Elia D, Goldstein JA, Eugster-Hausmann M. VAG-1748 trial investigators. Endometrial safety of ultra-low-dose Vagifen 10 mcg in postmenopausal women with vaginal atrophy. Climacteric. 2010;13(3):228–237.

Alternatives

- Replens – must use daily
- Repagyn suppository

Testosterone- we don't know effects!

- Both testosterone and estrogen have effects on sexual function
- Serum testosterone not useful for diagnosis of sexual dysfunction
- Transdermal testosterone may increase satisfactory sexual events. No products for this indication in canada.

Cognition

- Women at high risk of depression during transition
- Estrogen can help with major depression in perimenopause, not shown to help after menopause
- However, estrogen can augment SSRI's
- Verbal memory was thought to be less on E&P regardless of age

After Breast CA

- HABITS trial -2004

Terminated b/c increased risk of breast CA

Vaginal estrogen is controversial.

Very small dose little absorbed systemically

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Table 6.1. Estrogen preparations

Estrogen	Trade name	Strength	Comment
Oral, mg			
Conjugated estrogens	Premarin	0.3, 0.625, 1.25	
	CES	0.3, 0.625, 0.9, 1.25	
	Congest	0.3, 0.625, 0.9, 1.25, 2.5	
	PMS-conjugated estrogens	0.3, 0.625, 0.9, 1.25	
17β-estradiol (micronized)	Estrace	0.5, 1.0, 2.0	
Esterified estrogens	Estragyn	0.3, 0.625	
Transdermal			
Twice-weekly 17β-estradiol, μg	Estradiol Derm	50, 75, 100	
	Oesclim	25, 50	
	Estradot	25, 37.5, 50, 75, 100	
Weekly 17β-estradiol, μg	Climara	25, 50, 75, 100	
Daily 17β-estradiol, %	Estrogel (topical gel)	0.06	
	Divigel (topical gel)	0.1	Sachets contain 0.25, 0.5, or 1.0 g
Vaginal			
Conjugated estrogens	Premarin (cream)	0.625 mg/g	0.5 to 2.0 g/d
17β-estradiol	Estring (silicone elastomer ring)	2.0 mg/ring	
	Vagifem (vaginal tablet)	10 μg	Initial dose: 1 tablet/d for 2 wk Maintenance dose: 1 tablet twice per week, with 3- or 4-d interval
Estrone	Estragyn cream	0.1%	
Injectable			
Conjugated estrogens	Premarin	25 mg	
Estradiol valerate	PMS-estradiol valerate	10 mg/mL	

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Table 6.2. Progestogen preparations

Progestogen	Trade name	Strength	Comparable oral dose*
Oral, mg			
Medroxyprogesterone acetate	Apo-medroxy	2.5, 5, 10, 100	5.0
	Dom-medroxyprogesterone	2.5, 5, 10	
	Medroxy 2.5	2.5	
	Medroxy 5	5	
	PMS-medroxyprogesterone	2.5, 5, 10	
	Provera	2.5, 5, 10	
	Provera Pak 5	5 (14 tablets)	
	Provera Pak 10	10 (10 tablets)	
	Teva-medroxyprogesterone	2.5, 5, 10	
Megestrol	Megestrol	40, 160	5.0
	Megace OS	40/mL (liquid)	
Norethindrone	Micronor	0.35	0.7 to 1.0
Norethindrone acetate	Norlutate	5	1.0
Progesterone (micronized)	Prometrium	100	200
Intravaginal, mg			
Progesterone	Crinone 8% (gel)	90	
	Endometrin (insert)	100	
Injectable, mg/mL			
Medroxyprogesterone acetate	Depo-Provera	50 (5 mL) 150 (1 mL)	
	Medroxyprogesterone acetate injectable suspension	150 (1 mL)	
Progesterone	Progesterone Injection	50 (10 mL)	
Intrauterine, mg			
Levonorgestrel	Mirena Intrauterine System	52 per IUS	

*The Comparable oral dose for the various progestins is expected to have a similar effect on endometrium.[6]

Table 6.3. Combination products

Combination	Trade name	Strengths
Oral		
Conjugated estrogens (CE) and medroxyprogesterone acetate (MPA)	Premplus	0.625 mg CE + 2.5 mg MPA (2 tablets)
		0.625 mg CE + 5 mg MPA (2 tablets)
	Premplus cycle	0.625 mg CE (single tablet)
		0.625 mg CE + 10 mg MPA (2 tablets)
17β-estradiol (E_2) and drospirenone (DRSP)	Angeliq	1 mg E_2 + 1 mg DRSP
17β-estradiol (E_2) and norethindrone acetate (NETA)	Activelle	1 mg E_2 + 0.5 mg NETA
	ActivelleLD	0.5 mg E_2 + 0.1 mg NETA
Transdermal		
17β-estradiol (E_2) and levonorgestrel (LNG)	Climara Pro	45 µg E_2 + 15 µg LNG
17β-estradiol (E_2) and norethindrone acetate (NETA)	Estalis 140/50	50 µg E_2 + 140 µg NETA
	Estalis 250/50	50 µg E_2 + 250 µg NETA

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Table 9.2. Recommended websites

Organization	Website*
Natural Health Products Directorate, Health Canada	http://hc-sc.gc.ca/dhp-mps/prodnatur/index-eng.php Many links provide additional information on NHPs, including the Licensed Natural Health Products Database.
American Botanical Council	http://www.herbalgram.org An online resource for herbal news and information.
Cochrane Consumer Network	http://www.cochrane.org/consumers/homepage.htm Informs about consumer involvement in the Cochrane Collaboration.
European Scientific Cooperative on Phytotherapy (ESCOP)	http://www.escop.com An organization that aims to advance the scientific status of phytomedicines.
Memorial Sloan Kettering Cancer Center, New York	http://www.mskcc.org Provides information for oncologists and health care professionals, including a clinical summary for herbs, botanicals, and other products, with details about constituents, adverse effects, interactions, and potential benefits or problems. Also provides evaluations of alternative or unproved cancer therapies, as well as products for sexual dysfunction.
National Center for Complementary and Alternative Medicine, US National Institutes of Health	http://nccam.nih.gov Explores complementary and alternative healing practices in the context of rigorous science.
The Richard and Hinda Rosenthal Center for Complementary and Alternative Medicine	http://nyp.org/services/complementary.html Promotes an inclusive medical system by using scientific inquiry to ensure that the valuable health practices of other cultures are better understood and integrated with Western medical practices.

*Last accessed March 2014.

Table 9.3. Menopausal symptoms and NHPs: summary of main evidence-based findings

NHP	Type of evidence	Main findings
Phytoestrogens		
Isoflavones	3 systematic reviews[12–14]	Results still not conclusive. Supplements providing higher proportions of genistein or increased equol may provide more benefit.[15]
Flaxseed	4 RCTs	No benefit compared with placebo.[24–27]
Black cohosh	2 systematic reviews[40,41]	No significant effect compared with placebo or with HT on frequency or intensity of hot flashes and quality of life.
St. John's wort	1 clinical trial[46]	Significantly improved menopause-specific quality of life and reduced sleep difficulties. No significant effect on number and intensity of hot flashes.

helping reduce loss of bone mineral density when used in conjunction with adequate amounts of calcium and vitamin D and that it may reduce severe and frequent menopausal symptoms. A number of publications exist on red clover isoflavones that also indicate a modest effect in relieving menopausal symptoms, particularly when used at a dose of about 80 mg/d.[16–23] Products containing isoflavones sourced from soy and red clover and approved by Health Canada can be found by searching the Licensed Natural Health Products Database.

Three of the four studies evaluating the effect of flaxseed on menopausal symptoms reported no benefit compared with placebo.[24–27]

Although 2 systematic review results suggested a protective effect of isoflavones on bone density, a 2-year clinical trial found that isoflavone extract (200 mg once daily) was not superior to placebo in reducing bone loss or bone turnover in menopausal women.[28–30] A 1-year clinical trial did not show any effect of flaxseed, 40 g once daily, on femoral or lumbar bone mineral density.[24]

The effect of phytoestrogen subclasses, including isoflavone extracts and isoflavone food sources, on cardiovascular risk factors was the subject of a meta-analysis that was not limited to a menopausal population.[31] The analysis showed that long-term use of soy proteins significantly decreased diastolic blood pressure and levels of LDL cholesterol but