

Hormone Replacement Therapy

Seine Chiang, MD

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50 y.o. female with LMP 1 year ago and presents with complaints of “hot flushes”, vaginal dryness, irritability, and decrease libido. Sexually active, no contraception.

ROS: negative except for those noted above.

FHX: negative

Exam: BP nl, BMI 30 Normal except for presence of vulvovaginal atrophy

1. *What tests would you order on this patient and why?*

- FSH: if well over 40, patient can be reassured that contraception is not an issue. If FSH is between 20-40, counsel patient that she may still ovulate intermittently and may be at risk of unplanned pregnancy.
- TSH to rule out thyroid dysfunction
- Lipids: to assess cardiovascular risks as you consider possible HRT
- DEXA scan: to assess BMD. HRT is FDA approved for the prevention of osteoporosis, but not for treatment.
- Screening mammogram: insure that this is normal before considering instating HRT.
- +/- testosterone levels

2. *What is the most likely cause of this patient’s complaints?* Estrogen deficiency +/- androgen insufficiency.

3. *What are your therapeutic options?* Depends on what one is treating.

Estrogen: “hot flushes”, vaginal dryness, +/- irritability, hypoactive sexual desire

SSRI: “hot flushes”, irritability

Testosterone: +/-hypoactive sexual desire

4. *What is the most effective treatment of vasomotor symptoms?*

- 68-93% of menopausal women have hot flushes, beginning before menopause and peaking 2-3 years after.¹ “Flushes” often more severe in women after bilateral oophrectomy¹
- 30-50% have relief within weeks after initiating HT and if untreated, 80-90% of “flushes” resolve in 4 to 5 years.¹

<u>Drug</u>	<u>Starting Dose</u>	<u>% ↓ in “Flushes”^{1,2}</u>
Estrogen	0.625 CEE or equiv	80-100%
	0.45 CEE or equiv	60-80%
E+P	0.625 CEE+2.5 MPA	80-100%
	0.45 CEE+1.5 MPA	60-80%
Megestrol	20 mg/d	50-80%
Effexor(SSRIs)	75 mg / d	50-60%
Clonidine	0.1 mg bid	30-40%
Placebo, Herbal		30%

5. How do the findings in the HERS and WHI studies influence how you counsel patients about HRT?

As a secondary prevention trial, HERS showed that HRT should not be instituted to prevent CAD in women with known CAD, and that this highest risk for CV mortality occurred in the first year of use. As a primary prevention trial, the WHI showed that HRT was not effective as a primary prevention of CAD and again the greatest risk for CV event was during the first 1-2 yrs after instituting therapy. Neither study was designed to examine quality of life issues. The majority of these patients enrolled were older and did not have menopausal symptoms. Also, WHI showed that:⁵

<u>Events</u>	<u>E+P Risks</u>	<u>E-alone Risks</u>
CHD	↑ by 7	No difference
Strokes	↑ by 8	↑ by 12
PE	↑ by 8	Not reported
DVT	↑ by 18	↑ by 6
Breast Ca after 5 yrs of HRT use	↑ by 8	Poss ↓ by 7
Dementia	↑ by 23	↑ by 12
Hip fractures	↓ by 5	↓ by 6
Colorectal Cancer after 3 yrs of HRT use	↓ by 6	No difference

Based on these findings, the NIH, FDA, ACOG, and NAMs recommend that HRT is an effective option for the treatment of moderate to severe menopausal symptoms and should be prescribed for the shortest amount of time using the lowest effective dose.

6. How effective is vaginal estrogen therapy for symptoms of vulvovaginal atrophy?

<i>Variables</i>	<i>Treatment (n = 44)³</i>		<i>Control (n = 44)³</i>		<i>P*</i>
	<i>Before</i>	<i>After</i>	<i>Before</i>	<i>After</i>	
<i>Dryness</i>	100%	20.5%	100%	90.9%	<.001
<i>Dyspareunia</i>	86.4%	20.5%	84.1%	86.4%	<.001
<i>UG atrophy</i>	100%	27.3%	100%	93.2%	<.01

7. Is menopause associated with androgen-deficiency state? Can this explain her libido problem?

No, unless both ovaries were removed which would then lead to a 50% decline in bioavailable testosterone levels. Otherwise, androgen decline is age-dependent, not menopausal state dependent. For example, a 40 yo female has about 50% less androgens than a 20 yo female. The difference in androgens between a 45 yo female and a 55 yo female is insignificant. The postmenopausal ovary is an androgen-producing organ and since it no longer produces sufficient estradiol, the drop in serum estradiol results in decrease in SHBG, and subsequently in an increase in free testosterone. Other conditions that are may be associated with androgen deficiency include adrenal insufficiency or suppression, bilateral ovarian removal, oral estrogen use, hypopituitarism. See reference 4.

8. What are therapeutic options for the treatment of this patient's hypoactive sexual desire disorder?

None that are FDA-approved for the treatment of this condition. However, off-label options are available and include:

- Testosterone: Evidence-based data lacking and no guidelines available for use in menopausal women. You should consider documentation of androgen deficiency before use of these agents.
 - OTC DHEA (50 mg/day)
 - Compounding: 2% testosterone propionate in petrolatum, 0.5-1% testosterone cream
 - Esterified estrogen/Methyl testosterone (Estratest): this is FDA-approved only for the treatment of menopausal symptoms, not female sexual dysfunction.
- Estrogen: treat vulvovaginal atrophy symptoms with vaginal estrogen, consider switching to transdermal or transcutaneous estrogen if she is on oral estrogen (to minimize increase in SHBG and thereby increase bioavailable testosterone)
- Sildenafil: Efficacy in women not conclusive.

9. Assuming that the patient's FSH is 60, TSH, testosterone, Lipids, MMG, and DEXA are all normal, what are your management recommendations for this patient?

- Short-term low dose estrogen+progesterone, probably non-oral route of administration to minimize impact on SHBG and bioavailable testosterone.
- Vaginal estrogen (cream, ring, tablet): ↓symptoms of vulvovaginal atrophy and dyspareunia.
- Evaluate for other factors contributing to hypoactive sexual desire
- Weight loss and exercise to improve overall general well-being and maximize cardiovascular health.

10. How would you manage this patient if she has no improvement in her vasomotor symptoms after 2 months of therapy with CEE 0.9 mg, after increasing the dose from 0.625 mg?

If her TSH is normal, consider changing her to an equivalent dose of an estradiol product (rather than a CEE product) and measure serum estradiol after 2-3 weeks of therapy. If the estradiol levels are therapeutic (50-100), then consider the addition of low-dose SSRI for "psychogenic" vasomotor instability. If on the low end of therapeutic with persistent symptoms, consider small increase in dose or change to transdermal delivery.

References:

1. Grady, D *JAMA*, 2002 Vol. 287, No. 16
2. Utian, WH *Fertility & Sterility* 2001;75:1065-79
3. Dessole S, et al. *Menopause*. 2004;11:49-56.
4. Burger HG. *Menopausal Medicine* 13 (1), Spring 2005
5. www.WHL.org/Findings

Hormone Replacement Therapy Options. () are the different dosages available.

Estrogen+Progestin

- **Oral** Prempro ® (4), PremPhase ® (1), Activella ® (1), FemHRT ® (2)
- **Transdermal** Climara Pro ® (1), CombiPatch ® (2)

Estrogen Only

- **Oral** Premarin ®(5), Cenestin ® (4), Femtrace® (3), Ogen ®, Estrace® (3), **EstraTest** ® (2)
- **Transdermal** Climara® (6), Vivelle, Vivelle-Dot ® (5)
- **Topical** Estrasorb ® packets, EstroGel ® pump

Other: These agents do not result in significant serum levels of estrogen and do not require concomitant use of progestins if uterus is present.

- Estrace, Premarin creams, VagiFem Tablet ®, Estring ®