HRT of Menopausal transition and early menopausal women

Sung Hoon Kim, M.D.

Dept. of Obstetrics & Gynecology
University of Ulsan College of Medicine
Asan Medical Center

Terminology

- Recommended by the WHO in 1996

- *Natural menopause*

  Permanent cessation of menstruation resulting from the loss of ovarian follicular activity

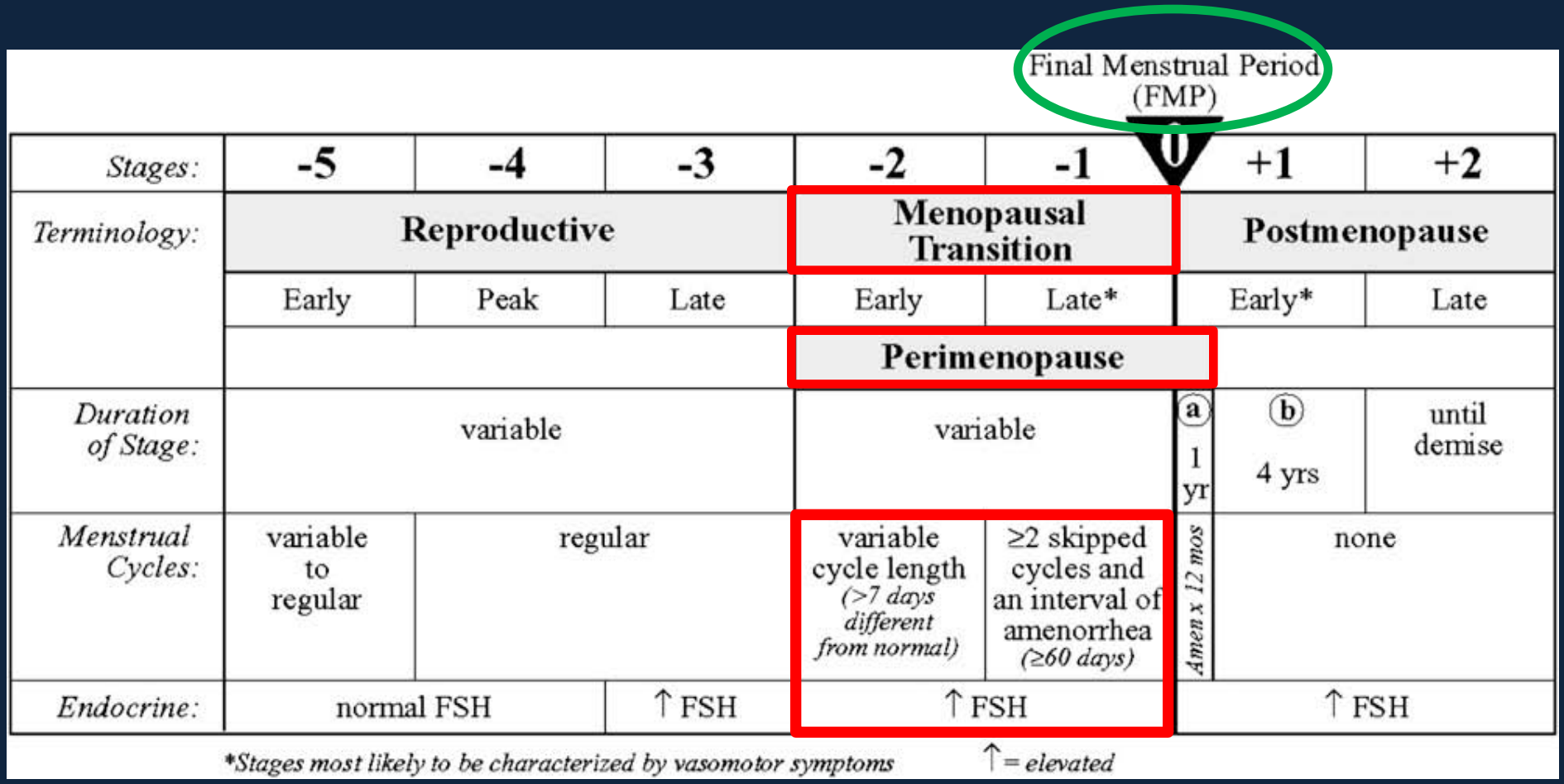
  After 12 consecutive months of amenorrhea without no other obvious pathologic or physiologic cause

- *Perimenopause :*

  Period immediately before the menopause and the first year after menopause.

STRAW Definition

Stages of Reproductive Aging Workshop (2001)



Stages:	-5	-4	-3	-2	-1	+1	+2
Terminology:	**Reproductive**			**Menopausal Transition**		**Postmenopause**	
	Early	Peak	Late	Early	Late*	Early*	Late
				Perimenopause			
Duration of Stage:	variable			variable		(a) 1 yr	(b) 4 yrs; until demise
Menstrual Cycles:	variable to regular	regular		variable cycle length *(>7 days different from normal)*	≥2 skipped cycles and an interval of amenorrhea *(≥60 days)*	*Amen x 12 mos*	none
Endocrine:	normal FSH		↑ FSH	↑ FSH		↑ FSH	

**Stages most likely to be characterized by vasomotor symptoms*

↑ = elevated

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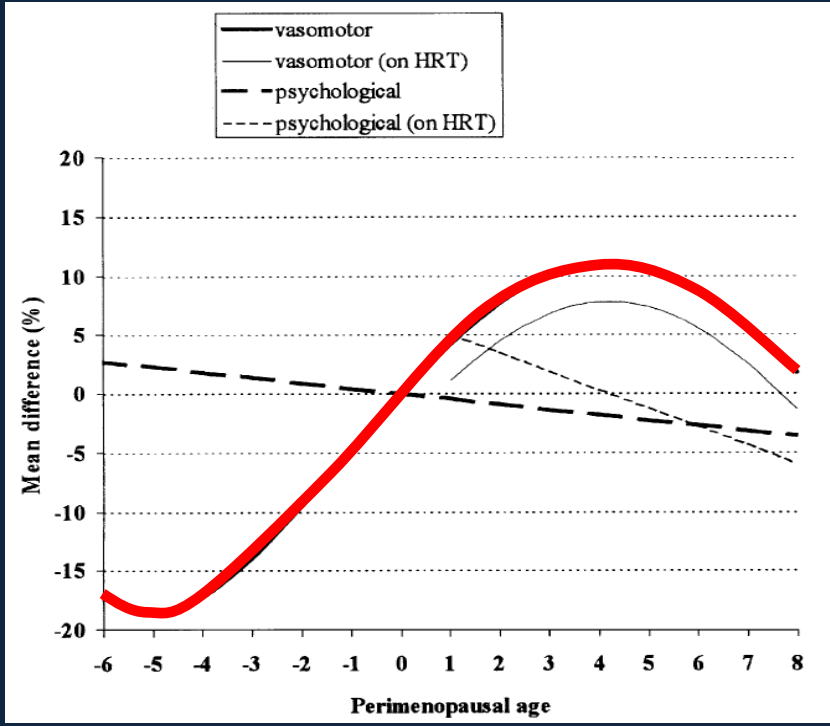
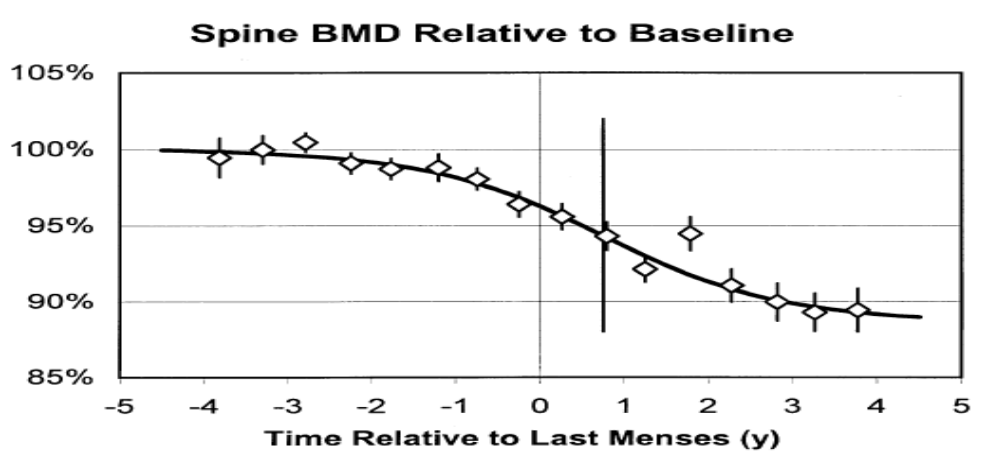
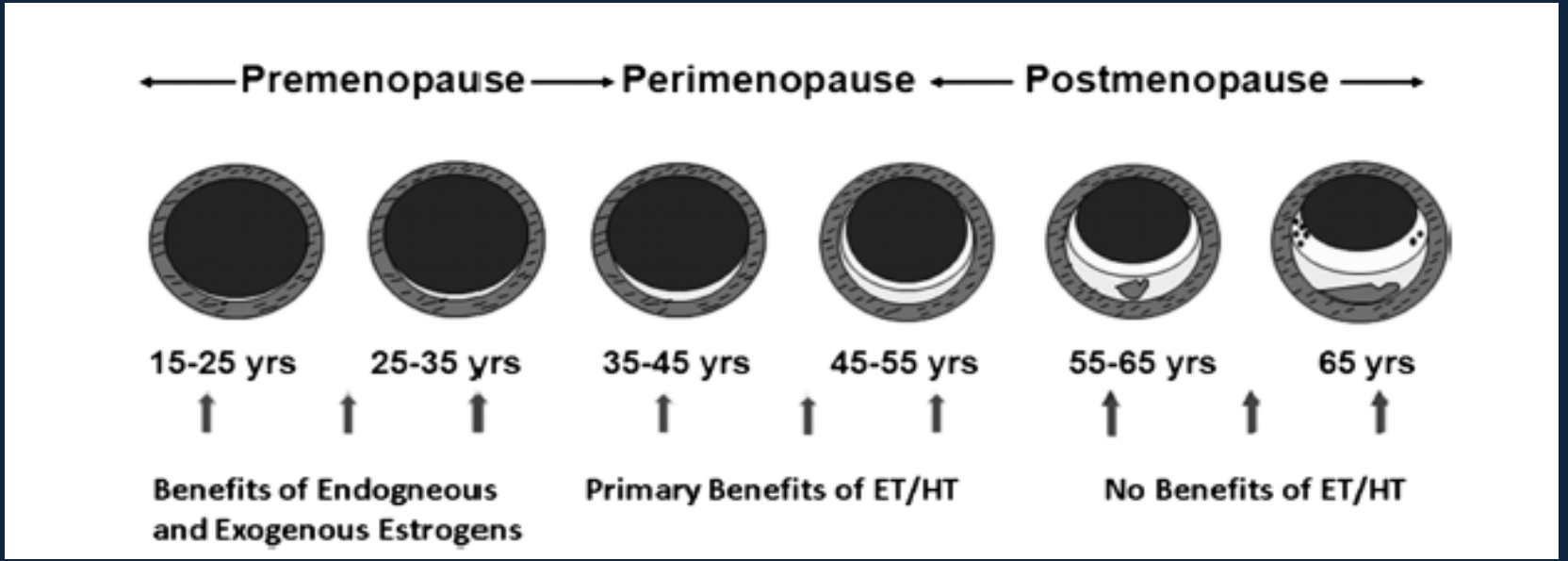
Importance of menopausal transition period





Timing hypothesis



HT initiated during perimenopausal transition or early menopause: slow the progression of lesions into larger, more complicated plaques.

Beneficial effects of HT will be lost several years after menopause

HRT of Menopausal transition and early menopausal women

- Endocrine change during perimenopausal period
- Management of Vasomotor symptom
- Management of DUB
- Osteoporosis prevention
- When to start HT?

Endocrine Changes

Table 1. Stages of the Menopausal Transition, Ranges of Hormone Levels, and the Prevalence of Hot Flushes.

Variable	Reproductive Years			Menopausal Transition (Perimenopause)		Postmenopausal Years	
	Early	Peak	Late	Early	Late	Early	Late
Menstrual cycle	Regular or variable	Regular		Variable cycle length; 1 or 2 missed cycles per yr	3 or more missed cycles per yr	None	
Range of steroid hormones (pg/ml)							
Estradiol	50–200			50–200 or slightly higher		40	0–15
Testosterone	400			400		400	400
Range of pituitary hormones (mU/ml)							
Follicle-stimulating hormone	10 on days 2–4			10 or higher on days 2–4		>100	
Luteinizing hormone	10 on days 2–4			10 or higher on days 2–4		>100	
Prevalence of hot flushes (%)			10	40	65	50	10–15

- Hot flush : prevalence increase through MT
- Prevalence varies markedly among studies.

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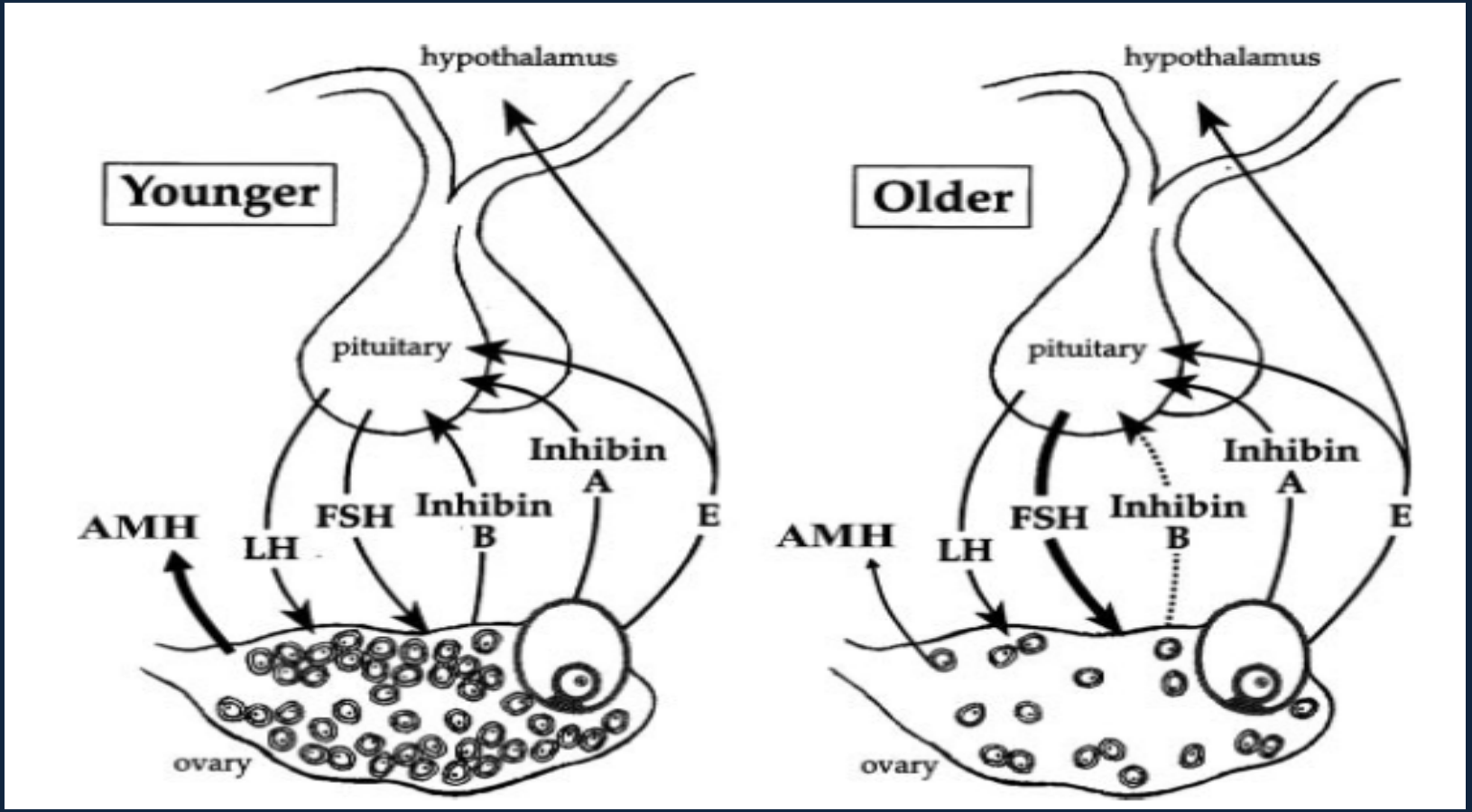
Endocrinology of late reproductive aging



F. J. Broekmans et al. Endocrine Reviews, August 2009, 30(5):465–493

Endocrinology of the menopausal transition

- Early menopausal transition:

  : Profound fall in the follicular phase concentrations of inhibin B with FSH levels being slightly raised

  :Cyclicity is for the most part preserved

  : highly variable patterns of gonadotropin and sex steroid output

Endocrinology of the menopausal transition

- Late menopausal transition :

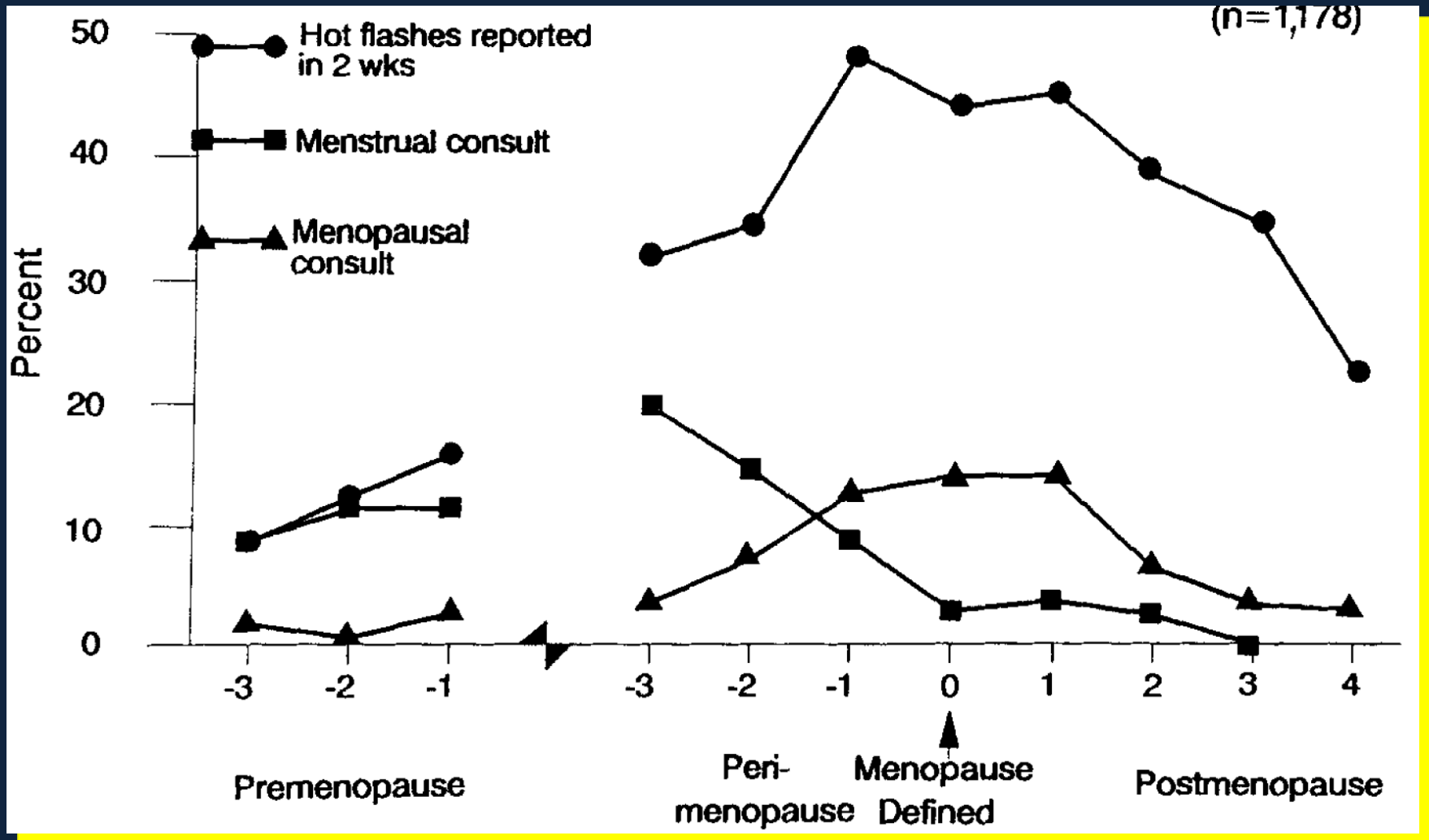
  : Marked falls in E2 and inhibin A together with significant elevations in FSH

- Follicle failure appears to occur, and sex steroid production wanes dramatically

- Eventually, menstrual cycles cease, but estrogen production occurs for a period of 6months to 2 years

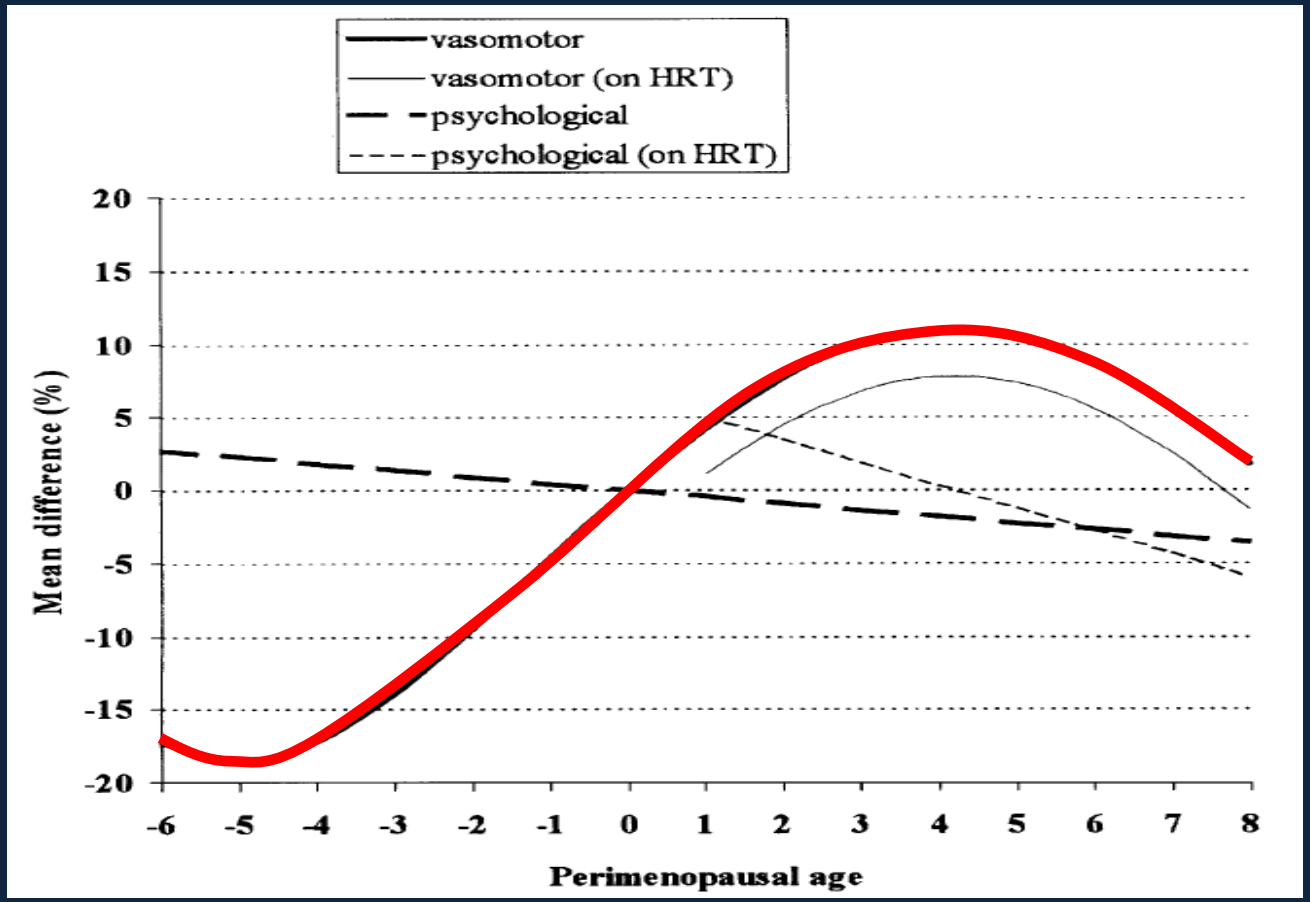
  →Steady state of hypergonadotropic hypogonadism

Clinical Issues in Perimenopause



Vasomotor Symptoms

- Mechanisms not fully understood.
- Vasomotor dysfunction : frequency, severity increase during MT (OR; 1.3-13)



Clinical Significance of VMS

- QoL (Hot Flush, Night sweat ...)
- Vascular endothelial dysfunction ➔ CVD risk

(2007, JAMA)

Table 6. Cardiovascular and Global Index Events in Subgroup of Participants with Moderate or Severe Vasomotor Symptoms at Baseline in the Combined Trials

	Age Group at Randomization									*P* Value	
	50-59 y			60-69 y			70-79 y				
	No. of Cases			No. of Cases			No. of Cases				
	Hormone Therapy (n = 1097)	Placebo (n = 1030)	HR (95% CI)*	Hormone Therapy (n = 691)	Placebo (n = 665)	HR (95% CI)*	Hormone Therapy (n = 197)	Placebo (n = 196)	HR (95% CI)*	Trend†	Interaction With Vasomotor Symptoms‡
CHD§	17	19	0.86 (0.44-1.65)	31	25	1.20 (0.70-2.04)	27	6	5.08 (2.08-12.40)	<.01	.04

Table 7. Cardiovascular and Global Index Events in Subgroup of Participants With Moderate or Severe Vasomotor Symptoms at Baseline in the Combined Trials

	Years Since Menopause									*P* Value	
	<10			10-19			≥20				
	No. of Cases			No. of Cases			No. of Cases				
	Hormone Therapy (n = 833)	Placebo (n = 757)	HR (95% CI)*	Hormone Therapy (n = 557)	Placebo (n = 555)	HR (95% CI)*	Hormone Therapy (n = 440)	Placebo (n = 459)	HR (95% CI)*	Trend†	Interaction With Vasomotor Symptoms‡
CHD§	13	17	0.84 (0.40-1.77)	17	13	1.38 (0.63-3.00)	39	16	2.76 (1.53-4.97)	<.01	.06

VMS & Depressive Symptoms

Table 2. Risk of First Onset of Depressive Symptoms in Premenopausal and Perimenopausal Women With No Lifetime History of Major Depression

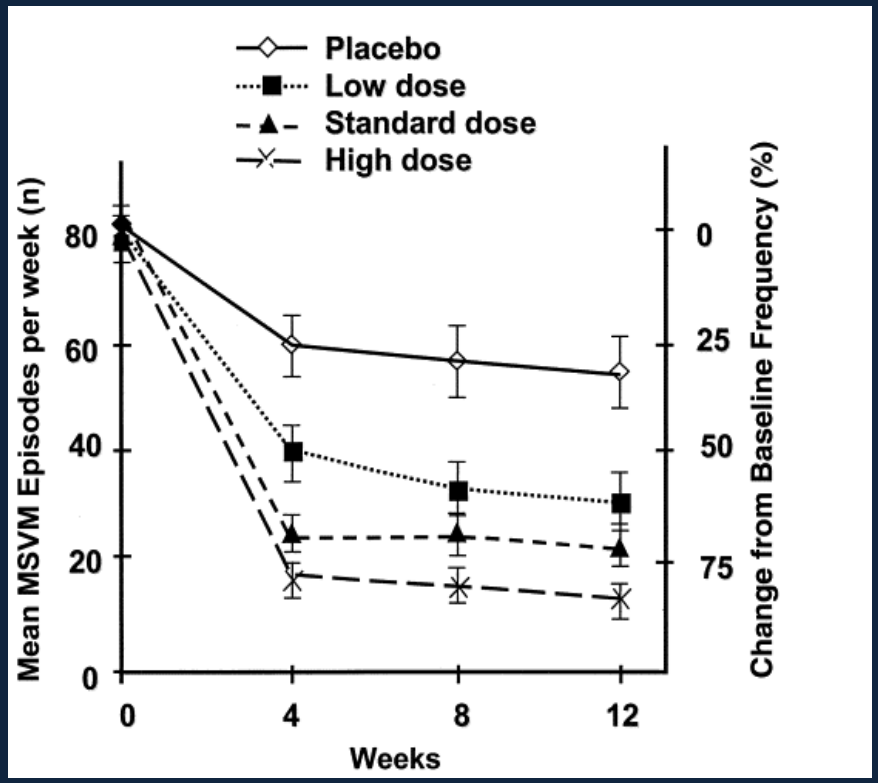
At Outcome or End of Follow-up	Any First Onset, No. (%)	Adjusted OR (95% CI)*	Severe First Onset, No. (%)†	Adjusted OR (95% CI)*
Premenopausal (n = 95)‡	19 (20.0)	1.0	9 (9.5)	1.0
Perimenopausal (n = 326)	106 (32.5)	1.8 (1.0-3.2)	54 (16.6)	1.9 (0.9-4.0)
No vasomotor symptoms (n = 169)§	52 (30.8)	1.8 (0.9-2.5)	23 (13.6)	1.6 (0.7-3.7)
Vasomotor symptoms (n = 135)	49 (36.3)	2.2 (1.1-4.2)	26 (19.3)	2.5 (1.1-5.8)
Unknown vasomotor symptoms (n = 22)	5 (22.7)	1.0 (0.3-3.3)	5 (22.7)	2.7 (0.8-9.1)
"Hormone-modulated" perimenopause (n = 49)‖	17 (34.7)	2.0 (0.9-4.5)	5 (10.2)	1.1 (0.4-3.7)
Natural perimenopause (n = 277)	89 (32.1)	1.8 (1.0-3.2)	49 (17.7)	2.0 (0.9-4.4)

Estrogen Deprivation : Hot flush

Table 2. Efficacy of Treatment of Hot Flushes with Various Doses of Estrogen, as Compared with Placebo.

Study Group	Reduction in Frequency of Hot Flushes
	*percent**
Oral conjugated equine estrogens (mg)[17]	
0.625	94
0.45	78
0.30	78
Placebo	44
Oral 17β-estradiol (mg)[18]	
2.0	96
1.0	89
0.5	79
0.25	59
Placebo	55
Transdermal 17β-estradiol (mg)[19]	
0.1	96
0.05	96
0.025	86
Placebo	45

Deborah et al. N Engl J Med 2006;355:2338-47.



Bruce et al. The American Journal of Medicine (2005) Vol 118 , 74S-78S

Estrogen Deprivation : Hot flush

The Hot Flush	
Premenopausal	10–25% of women
Perimenopausal	60%
Postmenopausal:	
No flushes	15–25%
Daily flushing	15–20%
Duration	1–2 years average
	5 or more years: 25%
Other Causes	Psychosomatic
	Stress
	Thyroid disease
	Subacute, chronic infections
	Pheochromocytoma
	Carcinoid
	Leukemia
	Cancer

- Estrogen deficiency as the cause of hot flushes should be documented by increased FSH.
- Prescribing estrogen inappropriately in the presence of normal levels of gonadotropins only temporarily postpones dealing with the underlying issues by a placebo response

Wilkin JK.Ann Intern Med. 1981Oct;95(4):468-76

Estrogen Deprivation : Hot flush

- Little response to large doses of estrogen

  ➔Careful inquiry for a basic psychoneurotic or psychosocial problem

- Measuring the patient's blood level of estradiol and showing the result

  ➔ Help persuade a patient that her symptoms not due to low levels of estrogen

Estrogen Deprivation : Hot flush

- The NAMS guideline 2004.

Mild vasomotor symptoms:

first consider lifestyle changes

either alone or combined with a nonprescription remedy

Moderate to severe hot flushes:

HRT is recommended as the therapeutic standard.

Progestins, SSRIs, or gabapentin

-suggested as an alternative for avoiding estrogens

Table 5. Evidence of the Efficacy of Nonestrogenic Prescription Drugs for the Treatment of Menopausal Hot Flushes from Randomized, Controlled Clinical Trials.*

Treatment	Oral Dose	Evidence of Benefit	Outcome†	Side Effects‡
Nonestrogen hormones				
Progestins				
MPA	20 mg daily	Yes	Improvement of 48% over placebo[30]	Nausea, vomiting, constipation, somnolence, depression, breast tenderness, and uterine bleeding; concern about increased risks of venous thromboembolism, cardiovascular events, and breast cancer
Megestrol	20 mg twice daily	Yes	Improvement of 47% over placebo in breast cancer survivors[31]	
Tibolone§	1.25 to 5.0 mg	Yes	Improvement of 35–50% over placebo[4,32]	Headache, weight gain, and uterine bleeding; unknown effects on venous thromboembolic events, cardiovascular disease, and breast and uterine cancer
Antidepressants				
SSRIs				Extensive list of side effects[37]¶
Citalopram	30 mg	No	No benefit over placebo[33]	
Fluoxetine	20 mg	Mixed	Improvement of 24% over placebo among breast cancer survivors[34]	
	30 mg		No benefit among women without breast cancer[33]	
Paroxetine	10 to 20 mg	Yes	Improvement of 30% over placebo among breast cancer survivors[35]	
	12.5 to 25 mg CR		Improvement of 25% over placebo among women without breast cancer[36]	
Sertraline		No	No benefit over placebo among breast cancer survivors[38]	
SNRIs				
Venlafaxine	75 or 150 mg	Mixed	Improvement of 34% over placebo among breast cancer survivors[39]	Same side effects as for SSRIs, but minimal effect on cytochrome P-450 enzymes (only slightly inhibits conversion of tamoxifen to active metabolites)[41]; possible hypertension
	75 mg ER		No benefit over placebo among women without breast cancer[40]	
Gabapentin	300 mg 3 times daily	Yes	Improvement of 31% over placebo among breast cancer survivors[42] and 23% over placebo among women without breast cancer[43]	Nausea, vomiting, somnolence, dizziness, rash, ataxia, fatigue, and leukopenia
Alpha-blockers				Dry mouth, drowsiness, dizziness, hypotension, and rebound hypertension
Clonidine	0.1 mg transdermal	Mixed	Little or no benefit[4,44] or improvement of 27% over placebo[45]	
Methyldopa	375 to 1125 mg daily in divided doses	No	No benefit over placebo[4]	

Deborah et al. N Engl J Med 2006;355:2338-47.

Vasomotor Symptoms

Trials in perimenopausal women

- Prospective observational study
  - 30μg EE of OC
  - after >2M, 90% patients complete relief

(1985, Shargil, Int J Fertil)

- Randomized, double-blind,
  - 20μg EE + norethindrone acetate 1mg
  - Severe Sx. reduced (50%)

(1997, Casper et al, Menopause)

- Sx. may occur during hormone free days.

DUB or AUB

- Irregular or heavy menstrual bleeding
- Premenopausal women with AUB, over age 45
  - EM pathology risk increased
  - OR 3.1 (95% CI, 1.5-6.1)

(1999, Farquhar et al, AJOG)

Table I. Independent risk factors for endometrial hyperplasia and carcinoma in women with abnormal bleeding (N = 1033)

	All abnormal histologic findings		*Complex, atypia, and carcinoma only*	
Risk factor	*Odds ratio and 95% confidence interval*	*Statistical significance*	*Odds ratio and 95% confidence interval*	*Statistical significance*
Weight ≥90 kg	5.5 (2.9-10.6)	$P < .0001$	7.3 (3.2-16.8)	$P < .0001$
Family history of colon cancer	5.0 (1.3-19.1)	$P = .0182$	9.1 (2.2-37.1)	$P = .002$
Infertility	3.6 (1.3-9.9)	$P = .0127$	3.3 (0.99-11.1)	$P = .051$
Age ≥45 y	3.1 (1.5-6.1)	$P = .0016$	NS	NS
Nulliparity	2.8 (1.1-7.2)	$P = .0267$	3.7 (1.2-10.9)	$P = .0193$
Family history of endometrial cancer	NS	NS	5.8 (1.1-28.6)	$P = .0392$

DUB or AUB

- Low dose OC recommended

① Prophylaxis against irregular, heavy anovulatory bleeding and the risk of endometrial hyperplasia and neoplasia

② Traditional postmenopausal hormone regimen without a contraceptive dose of progestin for the women not amenorrheic or without menopausal sx.

: Exposing EM to excessively high levels of estrogen
➔ risk of endometrial hyperplasia and neoplasia ↑
: Impossible to inhibit ovulation and contraception
➔ unexpected pregnancy

ACOG Practice Bulletin

- Combination OC is safe in healthy, nonsmoking.
- No increased risk of MI, stroke, breast cancer
- Positive effect on BMD
- Reduction of vasomotor symptoms
- Combination OC could be option for PM.

- Risk of VTE, CVD
  - Caution with obese, other CV disease
  - Should be individualized

(2006, Obstet Gynecol)

DUB or AUB

- Lowest estrogen dose OC available:
  4-fold greater than the standard postMP dose
  ➔ Dose-related risks with estrogen significant with increasing age

When to change from OC to postmenopausal HRT??

DUB or AUB

- Treatment free-week method

① annual measure the FSH level, beginning at age 50 (on day 6 or 7 of the estrogen-progestin-free week in a standard 3-week regimen)

② FSH >20IU/L ➔ change OC to HRT

- Empirical method :

① Empirically switching low dose estrogen-progestin contraception to postmenopausal HRT on midfifties

DUB or AUB

- Cochrane database review,2005

A progestin-containing intrauterine device (IUD) is another option that offers both control over bleeding and contraception

- Levonorgestrel IUS

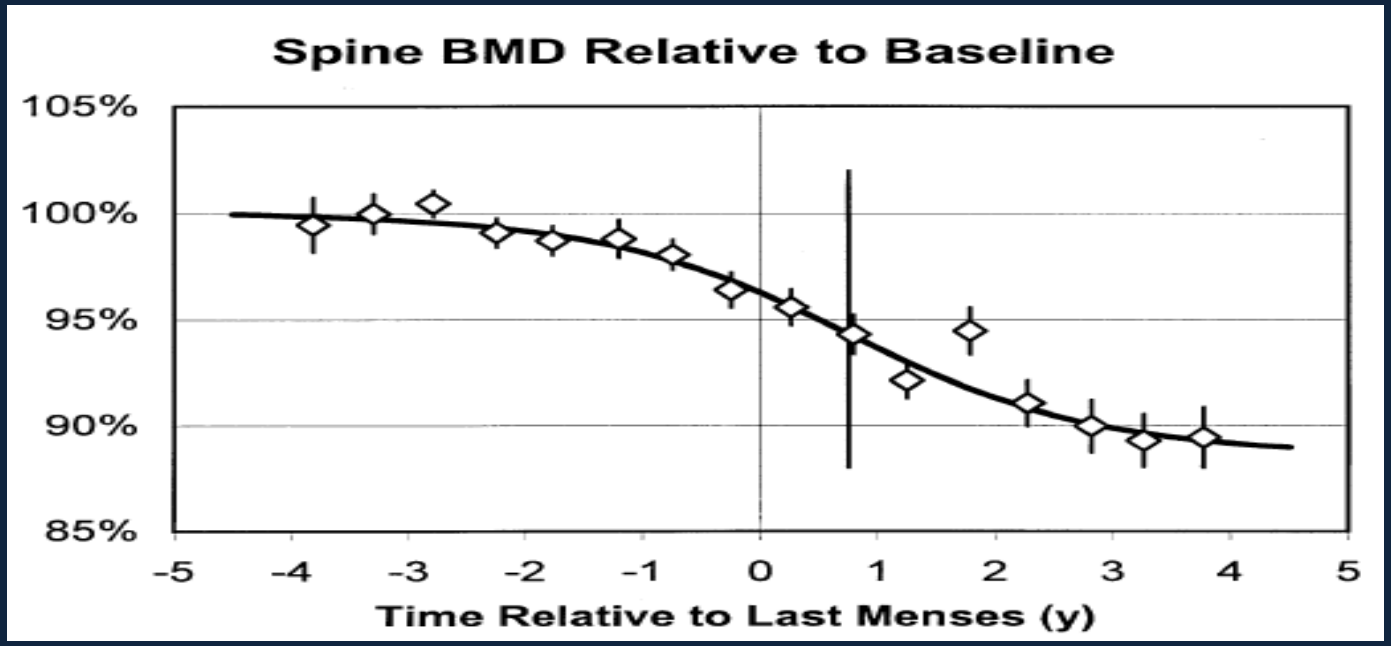
✓ Heavy vaginal bleeding
Similar effect & less side effect than oral progestin

✓ Tx of Endometrial hyperplasia
Similar and probably better effect than standard treatment with oral progestin

Osteoporosis

- Across menopause, sigmoid pattern of bone loss
- Begins 2-3yrs before MP, ends 3-4yrs after MP

(J Bone & mineral Res., 2000)



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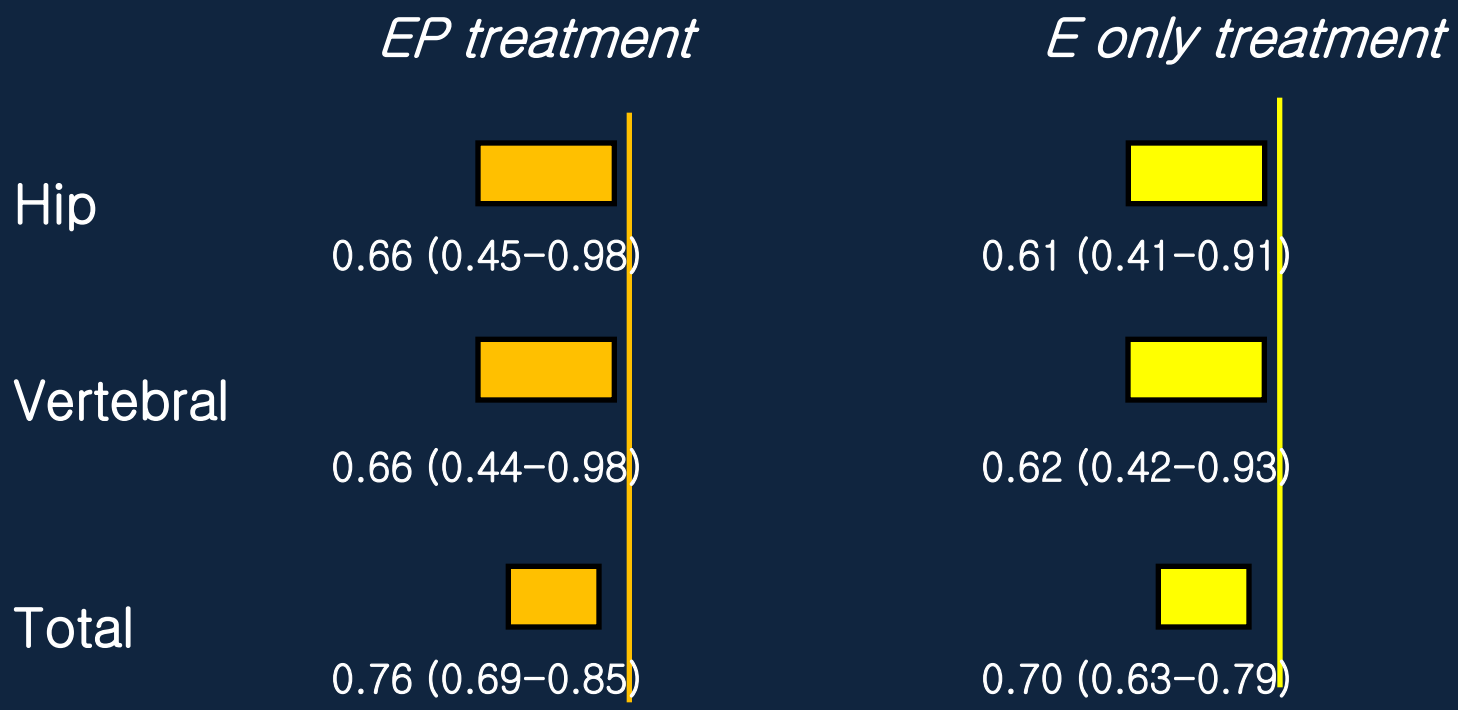
Skeletal Effects of HRT

- **WHI study, (2002 & 2004)**



The first trial with definite data supporting the ability of postmenopausal hormone to prevent fracture at the hip, vertebrae, and other sites.

BMD & Fracture

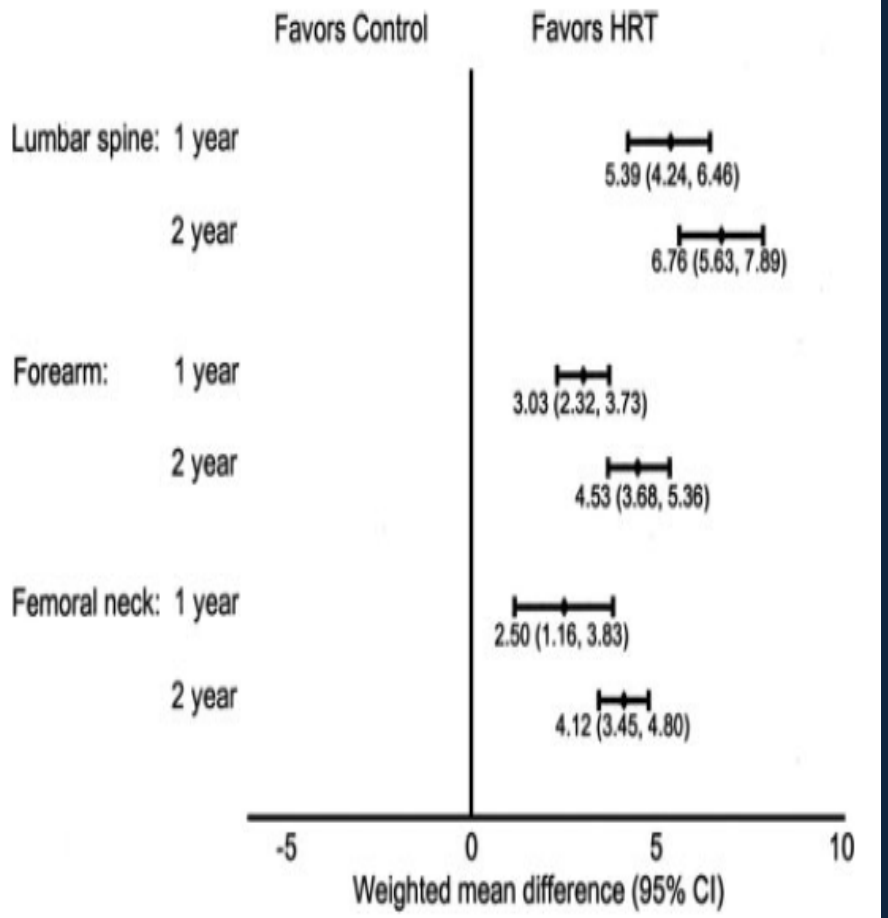


FIG. 1. Improvement in BMD with E+P therapy: a meta-analysis of 57

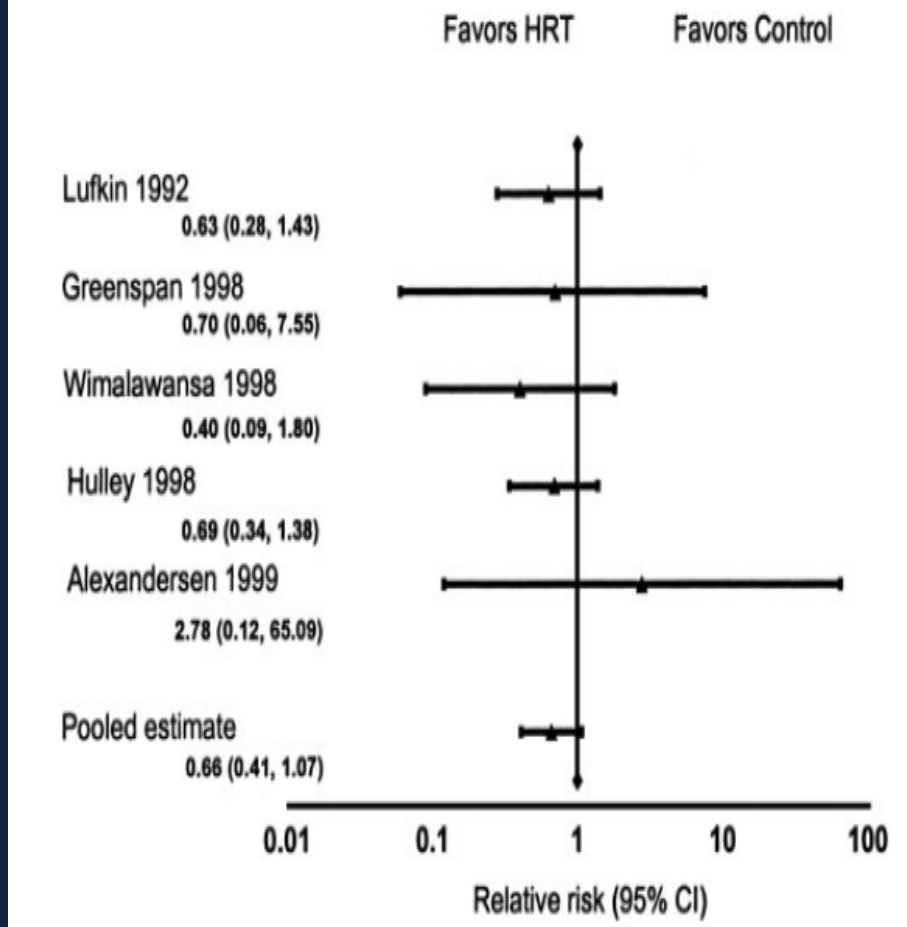


FIG. 3. RR of vertebral fracture after treatment with MHT. The *left*

OC decreased hip fracture

- OC preserve BMD.
- Longer duration, greater effect on BMD

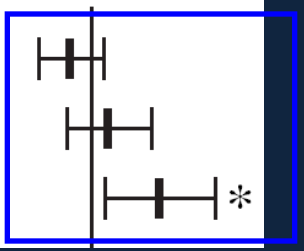
(Kritz-Silverstein 1993 Am J Public Health; Gambaccinani 1994 Maturitas)

Table I. Decreased hip fracture risk with oral contraceptive use

Age at oral contraceptive use	*Multivariate any oral contraceptive*	*Odds ratio (95% confidence interval) ≥50 µg ethinyl estradiol oral contraceptive*
Never used	1.0 (referent)	1.0 (referent)
<30 y	1.3 (0.8-2.1)	1.1 (0.6-2.0)
30-39 y	0.8 (0.6-1.2)	0.8 (0.5-1.1)
≥40 y	0.7 (0.5-0.9)	0.6 (0.4-0.9)

Timing hypothesis

CHD		
Years Since Menopause		
<10	0.18	0.24
10-19	0.43	0.39
≥20	0.78	0.62



Early Good, Late Bad?

Then, when to start HT?

When to start HT?

- When is early early enough?

  Late menopausal transition

  (time of accelerated atherosclerosis progression and endothelial dysfunction d/t Estrogen depletion)

- For menopausal sx control during menopausal transition : HRT > non hormonal drug

Thomas et al. Menopause: The Journal of The North American Menopause Society 2013;Vol. 20, No. 3, pp. 342/353

Recommendations

Expert Panel on Menopause in Asian Women

- Initiation during menopausal transition, greatest benefits

(2006, Climacteric)

NAMS Position Statement

- No specific recommendation confined to perimenopause
- HT initiation (proximal to MP) may be important.

(2010, Menopause)

The Endocrine Society

- No specific recommendation confined to perimenopause
- Menopausal women ages 50 to 59yr, benefits outweigh risks.

(2010, JCEM)

International Menopause Society

Maturitas 2008

- Initiation : for relief of menopausal sx

- Treatment by type of symptom during perimenopause
  - Menstrual disturbance : main symptom
    Progestogens during second half of cycle
    or LNG-IUS

  - If vasomotor symptom develop
    Sequential HRT or Estrogen + LNG-IUS

  - Contraception and/or cycle control
    Low-dose oral contraceptive

International Menopause Society

Maturitas 2008

During menopausal transition

- Sequential preparations
  - Relief from vasomotor symtoms
  - Achieve regular withdrawal bleeding
  - Sequential HRT or OC

- Usually after a minimum 1yr of last spontaneous menstruation period
  - bleed-free continuous combined estrogen/progestogen