

Estrogen Therapy

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References

Introduction

Estrogen, a steroid hormone, is derived from the androgenic precursors androstenedione and testosterone by means of aromatization. In order of potency, naturally occurring estrogens are 17 (beta)-estradiol (E2), estrone (E1), and estriol (E3). The synthesis and actions of these estrogens are complex.

In brief, estradiol is primarily produced by theca and granulosa cells of the ovary, and it is the predominant form of estrogen found in premenopausal women. Estrone is formed from estradiol in a reversible reaction. This is the predominant form of circulating estrogen after menopause. Estrone is also a product of the peripheral conversion of androstenedione secreted by the adrenal cortex. Estriol is the estrogen the placenta secretes during pregnancy. In addition, it is the peripheral metabolite of both estradiol and estrone; it is not secreted by the ovary.¹ Table 1 summarizes normal concentrations of the various estrogens.

Table 1. Production and Concentrations of Estrogens in Healthy Women¹

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Phase	17b-Estradiol		Estrone		Estriol	
	Serum Concentration, pg/mL	Daily Production, mg	Serum Concentration, pg/mL	Daily Production, mg	Serum Concentration, pg/mL	Daily Production, mg
Follicular	40-200	60-150	30-100	50-100	3-11	6-23
Pre-ovulatory	250-500	200-400	50-200	200-350	-	-
Luteal	100-150	150-300	50-115	120-250	6-16	12-30
Pre-menstrual	40-50	50-70	15-40	30-60	-	-
Post-menstrual	<20	5-25	15-80	30-80	3-11	5-22
Phase	17b-Estradiol		Estrone		Estriol	

	Serum Concentration, pg/mL	Daily Production, mg	Serum Concentration, pg/mL	Daily Production, mg	Serum Concentration, pg/mL	Daily Production, mg
Follicular	40-200	60-150	30-100	50-100	3-11	6-23
Pre-ovulatory	250-500	200-400	50-200	200-350	-	-
Luteal	100-150	150-300	50-115	120-250	6-16	12-30
Pre-menstrual	40-50	50-70	15-40	30-60	-	-
Post-menstrual	<20	5-25	15-80	30-80	3-11	5-22

Estrogens affect many different systems, organs, and tissues, including the liver, bone, skin, GI tract, breast, uterus, vasculature, and CNS. These effects appear to become most prominent during times of estrogen deficiency, such as the menopausal transition.

Menopausal Transition

Definition of menopause

[Menopause](#) is defined as the permanent cessation of menstrual periods that occurs naturally or that follows surgery, chemotherapy, or irradiation. Natural menopause is recognized after a woman has not had menses for 12 consecutive months and after another pathologic or physiologic (eg, lactation) causes are ruled out. The median age of women undergoing menopause is 52 years.²

Symptoms of menopause

During the menopausal transition, a reduction in ovarian function results in a number of symptoms. Symptoms secondary to changes in ovarian hormones can be difficult to distinguish from those due to general aging and/or other life changes.^{3,2} Symptoms often attributed to estrogen deficiency are many and vary in intensity among women. Symptoms most commonly reported during the menopausal transition include vasomotor symptoms, such as hot flashes and night sweats, vaginal and vulvar dryness, and sleep disturbances.

The prevalence of vasomotor symptoms is 14-51% in premenopausal women, 35-50% in perimenopausal women, and 30-80% in postmenopausal women.² Most women have hot flashes for 6 months to 2 years. However, one study group reported that 26% of women had hot flashes for 6-10 years, and 10% had them for more than 10 years.⁴ According to the Study of Women's Health Across the Nation (SWAN), the prevalence of vasomotor symptoms is highest among African-American women (46%), followed by Hispanic (34%), Caucasian (31%), Chinese (21%), and Japanese (18%) women.⁵

Other symptoms often attributed to menopause, but not necessarily well supported by data, include mood symptoms, cognitive disturbances, somatic symptoms, urinary incontinence, uterine bleeding problems, and sexual dysfunction. All of these may ultimately negatively affect the woman's overall quality of life.

Diseases occurring around the time of menopause

Menopause is also the time when the incidence and prevalence of other diseases, such as cardiovascular disease and osteoporosis, substantially increases. The effect of these conditions becomes important because women live long after menopause and hormone status directly impacts disease progression and manifestation.

Menopause and Hormone Therapy

Although decreasing estrogen levels alone do not cause all menopausal symptoms, estrogen—with or without progestogen (progesterone and progestin)—has been prescribed for many years to manage menopause. Estrogen was often prescribed to help alleviate symptoms of menopause, as well as to prevent cardiovascular disease (CVD) and osteoporosis. Some have recommended that the terminology be changed from hormone replacement therapy (HRT) to [hormone therapy](#), or HT, to reflect the shift in focus from replacing hormones to using them for symptomatic relief.²

Preparations

Several preparations are available for hormone therapy. They include estrogen therapy alone or estrogen in combination with a progestogen (EPT). Unopposed estrogen increases the likelihood of endometrial hyperplasia and [endometrial carcinoma](#).^{6,7} Prolonged use and, possibly, high doses are associated with increased risk of cancer.

When the effect of duration of use was evaluated, the relative risk (RR) ranged from 2.8 for 1-5 years of use to 9.5 for more than 10 years of use.⁶ Therefore, the addition of progestogen is advised for endometrial protection in women with a uterus. The exception is when low-dose estrogen is locally administered to treat vaginal atrophy.^{8,9} Of note, no long-term safety data are available regarding use of unopposed, low-dose local vaginal estrogen therapy.

Delivery systems

Preparations for estrogen therapy and EPT include oral, transdermal, injectable and vaginal formulations. Transdermal delivery systems include patches, gels, sprays, and lotions, while vaginal products include suppositories, creams, and rings.

Because of the potential risks and existing controversies regarding high-dose oral regimens, the popularity of low-dose preparations and different delivery systems (eg, transdermal patches, gels, and lotions) is increasing. One vaginal preparation, the estradiol acetate ring, delivers a systemic dose of estradiol.

Nonoral preparations avoid a first-pass hepatic effect. Therefore, they may not produce changes in lipids, clotting factors, and inflammatory markers. As a result, they may possibly decrease health risks and adverse effects. Recent data indicated that transdermal preparations were not associated with an increased risk of venous thromboembolism when they were compared with oral estrogen.¹⁰

EPT may be continuous (ie, daily administration of both estrogen and progestogen) or continuous sequential (ie, daily administration of estrogen, with progestogen added on certain days).

See Tables 2-4 for summaries of the available preparations in the United States (adapted from [NAMS](#) data). In addition to the preparations listed in the tables, an oral estrogen-testosterone product (Estratest, Estratest HS; Solvay Pharmaceuticals, Inc, Marietta, GA) is available in the United States but has not been approved by the US Food and Drug Administration.

Table 2. Products for Estrogen Therapy

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Oral Products			
Composition	Product Name	Available Doses, mg	
Conjugated estrogens	Premarin	0.3, 0.45, 0.625, 0.9, 1.25	
Synthetic conjugated estrogens	Cenestin	0.3, 0.45, 0.625, 0.9, 1.25	
	Enjuvia	0.3, 0.45, 0.625, 1.25	
Esterified estrogens	Menest	0.3, 0.625, 1.25, 2.5	
17 β -estradiol	Estrace	0.5, 1.0, 2.0	
	Various generics	0.5, 1.0, 2.0	
Estradiol acetate	Femtrace	0.45, 0.9, 1.8	
Estropipate (formerly piperazine estrone sulfate)	Ortho-Est	0.625, 1.25, 2.5	
	Ogen	0.625, 1.25, 2.5 (0.75 mg estropi-pate = 0.625 mg estrone)	
Transdermal and Topical Products			
17 β -Estradiol Formulation	Product Name	Estradiol Delivery Rate, mg/d	Frequency
Matrix patch	Alora	0.025, 0.05, 0.075, 0.1	Twice weekly
	Climara	0.025, 0.0375, 0.05, 0.075, 0.1	Once weekly
	Esclim	0.025, 0.0375, 0.05, 0.075, 0.1	Twice weekly
	Menostar	0.014	Once

			weekly
	Vivelle	0.025, 0.0375, 0.05, 0.075, 0.1	Twice weekly
	Vivelle-Dot	0.025, 0.0375, 0.05, 0.075, 0.1	Twice weekly
Reservoir patch	Estraderm	0.05, 0.1	Twice weekly
Transdermal gel	EstroGel 0.06%	0.035	Daily, metered pump
	Elestrin 0.06%	0.0125	Daily, metered pump
	Divigel 0.1%	0.003, 0.009, 0.027 (available dose packets 0.25, 0.5, or 1.0 g)	Daily
Topical emulsion	Estrasorb	0.05 (3.48 g/d)	Daily
Transdermal spray	Evamist (1.7%, metered dose)	1.53 mg/spray	Initial: 1 spray/day Maintenance: 1-3 spray/day
Vaginal Products			
Formulation	Composition	Product Name	Dosing
Cream	17 β -estradiol	Estrace	Initial: 2-4 g/day for 1-2 wks Maintenance: 1 g 1-3 times/wk (1 g = 0.1 mg estradiol)
	Conjugated estrogens	Premarin	Initial: 0.5–2 g/d for 1-2 wk Maintenance: 1-3 times/wk (1 g = 0.625 mg estrogen)
Vaginal ring	17 β -estradiol	Estring	Releases 7.5 μ g/d; 90 d
	Estradiol acetate	Femring (systemic)	Releases 0.05 mg/d or 0.10 mg/d; 90 d

Vaginal tablet	Estradiol hemihydrate	Vagifem	25 µg Initial: 1 tab/d for 2 wk Maintenance: 1 tab twice/wk
Oral Products			
Composition	Product Name	Available Doses, mg	
Conjugated estrogens	Premarin	0.3, 0.45, 0.625, 0.9, 1.25	
Synthetic conjugated estrogens	Cenestin	0.3, 0.45, 0.625, 0.9, 1.25	
	Enjuvia	0.3, 0.45, 0.625, 1.25	
Esterified estrogens	Menest	0.3, 0.625, 1.25, 2.5	
17β-estradiol	Estrace	0.5, 1.0, 2.0	
	Various generics	0.5, 1.0, 2.0	
Estradiol acetate	Femtrace	0.45, 0.9, 1.8	
Estropipate (formerly piperazine estrone sulfate)	Ortho-Est	0.625, 1.25, 2.5	
	Ogen	0.625, 1.25, 2.5 (0.75 mg estropi-pate = 0.625 mg estrone)	
Transdermal and Topical Products			
17 β -Estradiol Formulation	Product Name	Estradiol Delivery Rate, mg/d	Frequency
Matrix patch	Alora	0.025, 0.05, 0.075, 0.1	Twice weekly
	Climara	0.025, 0.0375, 0.05, 0.075, 0.1	Once weekly
	Esclim	0.025, 0.0375, 0.05, 0.075, 0.1	Twice weekly

	Menostar	0.014	Once weekly
	Vivelle	0.025, 0.0375, 0.05, 0.075, 0.1	Twice weekly
	Vivelle-Dot	0.025, 0.0375, 0.05, 0.075, 0.1	Twice weekly
Reservoir patch	Estraderm	0.05, 0.1	Twice weekly
Transdermal gel	EstroGel 0.06%	0.035	Daily, metered pump
	Elestrin 0.06%	0.0125	Daily, metered pump
	Divigel 0.1%	0.003, 0.009, 0.027 (available dose packets 0.25, 0.5, or 1.0 g)	Daily
Topical emulsion	Estrasorb	0.05 (3.48 g/d)	Daily
Transdermal spray	Evamist (1.7%, metered dose)	1.53 mg/spray	Initial: 1 spray/day Maintenance: 1-3 spray/day
Vaginal Products			
Formulation	Composition	Product Name	Dosing
Cream	17 β -estradiol	Estrace	Initial: 2-4 g/day for 1-2 wks Maintenance: 1 g 1-3 times/wk (1 g = 0.1 mg estradiol)
	Conjugated estrogens	Premarin	Initial: 0.5–2 g/d for 1-2 wk Maintenance: 1-3 times/wk (1 g = 0.625 mg estrogen)
Vaginal ring	17 β -estradiol	Estring	Releases 7.5 μ g/d; 90 d
	Estradiol acetate	Femring	Releases 0.05 mg/d or

		(systemic)	0.10 mg/d; 90 d
Vaginal tablet	Estradiol hemihydrate	Vagifem	25 µg Initial: 1 tab/d for 2 wk Maintenance: 1 tab twice/wk

Table 3. Progestogens Used for Hormone Therapy

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Route	Drug, Formulation	Composition	Product Name	Available Doses, mg
Oral	Progestin, tablet	Medroxypro-gesterone acetate	Provera, generics	2.5, 5, 10
		Norethindrone	Micronor, Nor-QD, generics	0.35
		Norethindrone acetate	Aygestin, generics	5
		Norgestrel	Ovrette	0.075
		Megestrol acetate	Megace, generics	20, 40
	Progesterone, capsule	Progesterone in peanut oil, micronized	Prometrium	100, 200
Intrauterine	Progestin, system	Levonorgestrel	Mirena	20 µ g/d, 5-y use
Vaginal	Progesterone, gel	Progesterone	Prochieve 4%	45 mg/ applicator
			Crinone 4%, 8%	45 or 90 mg/ applicator
Route	Drug, Formulation	Composition	Product Name	Available Doses, mg
Oral	Progestin, tablet	Medroxypro-gesterone acetate	Provera, generics	2.5, 5, 10
		Norethindrone	Micronor, Nor-QD, generics	0.35

		Norethindrone acetate	Aygestin, generics	5
		Norgestrel	Ovrette	0.075
		Megestrol acetate	Megace, generics	20, 40
	Progesterone, capsule	Progesterone in peanut oil, micronized	Prometrium	100, 200
Intrauterine	Progestin, system	Levonorgestrel	Mirena	20 µ g/d, 5-y use
Vaginal	Progesterone, gel	Progesterone	Prochieve 4%	45 mg/ applicator
			Crinone 4%, 8%	45 or 90 mg/ applicator

Table 4. Estrogen–Progestogen Combination Products

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Regimen	Composition*	Product Name	Available Doses & Dosing*	
Oral continuous cyclic	Conjugated estrogens (E) + medroxyprogesterone acetate (P)	Premphase	0.625 mg E + 2.5 or 5.0 mg P, 0.3 or 0.45 mg E + 1.5 mg P	
Oral continuous combined	Conjugated estrogens (E) + medroxyprogesterone acetate (P)	Prempro	0.625 mg E + 2.5 or 5.0 mg P, 0.3 or 0.45 mg E + 1.5 mg P	
	Ethinyl estradiol (E) + norethindrone acetate (P)	Femhrt	5 µg E + 1 mg P, 2.5 µg E + 0.5 mg P	
	17 β -estradiol (E) + norethindrone acetate (P)	Activella	1 mg E + 0.5 mg P, 0.5 mg E + 0.1 mg P	
	17 β -estradiol (E) + drospirenone (P)	Angeliq	1 mg E + 0.5 mg P	
Oral intermittent combined	17 β -estradiol (E) + norgestimate (P)	Prefest	1 mg E + 0.09 mg P; E alone for 3 d, E + P for 3 d, repeat	
Transdermal continuous combined	17 β -estradiol (E) + norethindrone acetate (P)	Combi-Patch	0.05 mg E + 0.14 mg P,	Twice weekly

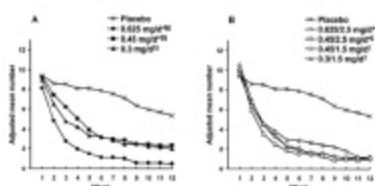
			0.05 mg E + 0.25 mg P	
	17 β -estradiol (E) + levonorgestrel (P)	Climara Pro	0.045 mg E + 0.015 mg P	Once weekly
* E = estrogen component; P = progesterone component				
Regimen	Composition*	Product Name	Available Doses & Dosing*	
Oral continuous cyclic	Conjugated estrogens (E) + medroxypro- gesterone acetate (P)	Premphase	0.625 mg E + 2.5 or 5.0 mg P, 0.3 or 0.45 mg E + 1.5 mg P	
Oral continuous combined	Conjugated estrogens (E) + medroxypro-gesterone acetate (P)	Prempro	0.625 mg E + 2.5 or 5.0 mg P, 0.3 or 0.45 mg E + 1.5 mg P	
	Ethinyl estradiol (E) + norethindrone acetate (P)	Femhrt	5 μ g E + 1 mg P, 2.5 μ g E + 0.5 mg P	
	17 β -estradiol (E) + norethindrone acetate (P)	Activella	1 mg E + 0.5 mg P, 0.5 mg E + 0.1 mg P	
	17 β -estradiol (E) + drospirenone (P)	Angeliq	1 mg E + 0.5 mg P	
Oral intermittent combined	17 β -estradiol (E) + norgestimate (P)	Prefest	1 mg E + 0.09 mg P; E alone for 3 d, E + P for 3 d, repeat	
Transdermal continuous combined	17 β -estradiol (E) + norethindrone acetate (P)	Combi-Patch	0.05 mg E + 0.14 mg P, 0.05 mg E + 0.25 mg P	Twice weekly
	17 β -estradiol (E) + levonorgestrel (P)	Climara Pro	0.045 mg E + 0.015 mg P	Once weekly
* E = estrogen component; P = progesterone component				

Hormone Therapy and Vasomotor Symptoms

Estrogen therapy, with or without a progestogen, has long been prescribed to treat menopausal symptoms. It has been extensively studied, and it is the most consistently effective therapy for vasomotor symptoms.² Data from numerous studies suggest that oral, transdermal, or vaginal hormone therapy reduces the severity of hot

flashes by 65-90%.^{11,12,13,14,15,16,17,18,19} The available data do not suggest that different types of estrogens (eg, conjugated estrogens vs estradiol) differ in efficacy.¹⁴

Data also indicate that low-dose preparations are effective in reducing both the severity and the number of hot flashes compared with commonly prescribed doses, though a dose-response relationship may be observed (see following image).²⁰ Low-dose estrogen is often considered to be 0.3 mg or less of conjugated estrogen, 0.5 mg or less of oral micronized estradiol, 2.5 mcg or less of ethinyl estradiol, or 25 mcg or less of transdermal estradiol.



Mean daily number of hot flashes by week for various doses of conjugated estrogen (CEE) alone or combined with medroxyprogesterone acetate (MPA). (Utian, 2001) A, Placebo and CEE groups; B, Placebo and CEE-MPA groups.

Difference vs placebo was significant ($P < .05$) from weeks *2-12 or †3-12. ‡Difference between CEE 0.45 mg/d and CEE 0.45 mg/d with MPA 2.5 mg/d was significant ($P < .05$) at weeks 3, 4, 5, and 9. §Difference between CEE 0.625 vs 0.45 mg/d was significant ($P < .05$) from weeks 2-12. ¶Difference between CEE 0.625 and 0.3 mg/d was significant ($P < .05$) at weeks 4, 5, 6, 9, 10, and 12.

Differences between high- and low-dose preparations tend to be greatest at 4 weeks after the start of hormone therapy and are reduced after 8-12 weeks. Low-dose preparations are desirable because they may be safer than high-dose forms in terms of CVD, venous thromboembolism, stroke, and breast cancer. In addition, they also decrease unacceptable adverse effects, such as irregular bleeding and breast tenderness.

Women who are starting low-dose estrogen therapy should be counseled that it may take 8-12 weeks for their vasomotor symptoms to be relieved (see above image).^{21,22} If a low-dose estrogen is selected, a low dose of progestogen can also be prescribed. This reduction can be accomplished either by decreasing the daily dose or by increasing the interval between cycles. No current guidelines have been established. However, low doses of oral medroxyprogesterone acetate (ie, 1.5 mg/d), when combined with low doses of oral conjugated estrogen (0.30-0.45 mg/d), provide adequate endometrial protection.²³ Likewise, a low dose of norethisterone acetate (0.125 mg/d), when combined with estradiol (0.025 mg/d) in a transdermal preparation, also provides endometrial protection.²⁴

Furthermore, if low-dose estrogens are used with cyclic progestogen regimens, intervals between progestogen use can be lengthened without significantly compromising endometrial protection. Examples of this approach include using medroxyprogesterone acetate 10 mg/day for 14 days every 3 months²¹ or every 6 months.²⁵

For a variety of reasons, some women do not wish to take hormones and are more interested in herbal products. In recent comparisons of oral estrogen therapy (0.625 mg of conjugated estrogen with or without medroxyprogesterone acetate 2.5 mg/d) versus a variety of herbal supplements, hormone therapy was the only treatment that reduced vasomotor symptoms.²⁶ Herbal formulations that have been shown to reduce symptoms with short-term use mostly contain black cohosh.

Hormone Therapy and the Prevention of Cardiovascular Disease

Results from epidemiologic studies in the 1980s and 1990s, such as the Nurses' Health Study, suggested that hormone therapy was protective against coronary heart disease (CHD) and related mortality.^{27,28} Data from retrospective studies also supported the notion that hormone therapy was cardioprotective.²⁹ Indeed, findings from a meta-analysis suggested that hormone therapy decreased the risk of CVD in women by 40-50%.³⁰ The conclusion from another meta-analysis was that hormone therapy should probably be recommended for women who have undergone a hysterectomy and for those with CHD or who are at high risk of CHD.³¹

In fact, the data regarding the multiple benefits of hormone therapy were so convincing that a 1998 American College of Obstetricians and Gynecologists (ACOG) Educational Bulletin stated, "Hormone replacement therapy should be considered to relieve vasomotor symptoms, genital urinary tract atrophy, and mood and cognitive disturbances, as well as to prevent osteoporosis and cardiovascular disease."³² Of note, the bulletin did mention that these perceived benefits must be assessed against the potential increased risk of breast cancer.

The mechanism thought to mediate this reduction in CVD is the beneficial effects on lipids and lipoproteins, particularly increased high-density-lipoprotein cholesterol, and decreased low-density lipoprotein-cholesterol concentrations.^{33,34} Also noted are reductions in fibrinogen, fasting glucose, and insulin levels,³³ as well as beneficial effects on arterial walls.³⁵ The effects of hormone therapy on hemostatic variables are complex, and the data are conflicting.³⁶

Current Controversy With Hormone Therapy

Estrogen therapy for perimenopausal and postmenopausal women became controversial with the publication of reports from 2 randomized clinical trials: the Heart and Estrogen/Progestin Replacement Study (HERS), a secondary prevention study,³⁷ and the Women's Health Initiative (WHI), a primary prevention study.

HERS was the first randomized, placebo-controlled, double-blind trial to study the effect of hormone therapy on CVD. Study subjects included more than 2700 postmenopausal women with a history of CHD. The hypothesis was that women who already had diagnosed CHD benefit most from hormone therapy. All women had a uterus and were randomly assigned to receive 0.625 mg of conjugated estrogen plus 2.5 mg of medroxyprogesterone acetate, or placebo. Women were observed for 4.1 years. The study was then unblinded, and some of the women were observed for an additional 2.7 years in HERS II.³⁸

Investigators from HERS and HERS II concluded that postmenopausal hormone therapy offered no CVD benefit among women with established disease, though it did improve lipid profiles. Additional venous thromboembolic events were also documented in women using hormone.

The WHI was a large clinical trial of healthy postmenopausal women (age range, 50-79 y; mean, 63.2 y). It was designed to evaluate the effects on CHD of 0.625 mg of conjugated estrogen with or without 2.5 mg of medroxyprogesterone acetate. The effects of estrogen on fractures, breast cancer, and venous thrombosis were also evaluated. The WHI Memory Study (WHIMS), a subanalysis of the WHI, was conducted to evaluate the effects of hormone therapy on cognition and dementia. The WHI is purported to be the definitive study of hormone use in healthy postmenopausal women.

In July 2002, researchers announced that the combined estrogen-progestin arm of the WHI was stopped early (after 5.2 y) because of an increased incidence of breast cancer in the hormone group compared with the placebo group. Increases were also reported in blood clots, stroke, and heart disease in the hormone group. In

February 2004, the estrogen-only arm of the WHI was stopped because of an increased risk of stroke and because estrogen failed to reduce the risk of CHD, which was the key outcome variable of the trial.

The major finding of both the HERS and the WHI was that hormone therapy should not be prescribed to prevent CVD.

Table 5 shows results of the WHI for both the combined estrogen-progestin and estrogen-only groups.

Table 5. Risks and Benefits for Hormone Therapy in the WHI Hormone Trial.³⁹

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Event	Estrogen Plus Progestin vs Placebo			Estrogen Alone vs Placebo		
	Hazard Ratio	Events/10,000 Women/y		Hazard Ratio	Events/10,000 Women/y	
		Increase	Decrease		Increase	Decrease
CHD ^{40, 41}	1.24	+6	NA	0.95	NA	-3
Breast cancer ^{42, 43}	1.24	+8	NA	0.80	NA	-6
Stroke ^{44, 45}	1.31	+7	NA	1.37	+13	NA
Venous thrombo-embolism ^{46, 47}	2.06	+18	NA	1.32	+8	NA
Colorectal cancer ^{48, 39}	0.56	NA	-6	1.08	+1	-6
Hip fracture ^{49, 39}	0.67	NA	-5	0.61	NA	-56
Total fractures ^{49, 39}	0.76	NA	-47	0.70	NA	
NA = not applicable						
Event	Estrogen Plus Progestin vs Placebo			Estrogen Alone vs Placebo		
	Hazard Ratio	Events/10,000 Women/y		Hazard Ratio	Events/10,000 Women/y	
		Increase	Decrease		Increase	Decrease
CHD ^{40, 41}	1.24	+6	NA	0.95	NA	-3
Breast cancer ^{42, 43}	1.24	+8	NA	0.80	NA	-6

Stroke ^{44, 45}	1.31	+7	NA	1.37	+13	NA
Venous thrombo-embolism ^{46, 47}	2.06	+18	NA	1.32	+8	NA
Colorectal cancer ^{48, 39}	0.56	NA	-6	1.08	+1	-6
Hip fracture ^{49, 39}	0.67	NA	-5	0.61	NA	-56
Total fractures ^{49, 39}	0.76	NA	-47	0.70	NA	
NA = not applicable						

Many questions remain regarding the effects of hormone therapy on CVD. Both methodologic and biologic reasons have been proposed to explain the conflicting results of observational studies and clinical trials.⁵⁰ Critics of the WHI point to the mean age of the women in the study (63 y) and to when hormone therapy was started in relation to the onset of menopause.^{9,51} Many women in the WHI started taking hormone therapy more than 10 years after menopause.⁵²

Some hypothesize that differences in the underlying vascular biology between perimenopausal women and older women may be important in understanding the available data.⁵³ The age when women begin hormone therapy is likely relevant. Indeed, data from animal studies suggest the cardioprotective effects of hormone therapy occur only when it is started before advanced atherosclerosis develops, when estrogen produces beneficial changes in endothelial function. After this time, estrogen may trigger cardiac events by means of inflammatory and procoagulant mechanisms.^{53,52} Therefore, a window of opportunity may exist for cardioprotection.

Of interest, age-group data showed a trend of lowered CHD risk in the estrogen therapy arm of the WHI for women aged 50-59 years.⁴⁰ The hazard ratios for myocardial infarction or coronary death were 0.61 for women aged 50-59 years, 0.86 for women aged 60-69 years, and 1.10 for women aged 70-79 years. The difference for this lowered risk was not statistically significant, but this may have resulted because of the low event rate in the age group. The frequency of coronary revascularization was decreased in women aged 50-59 years who were taking estrogen therapy; this difference was statistically significant.

In another secondary analysis of the WHI data, researchers evaluated the effects of hormone therapy on CHD according to years since menopause by using statistical techniques to improve power.⁵² This reanalysis provided clinical data to support the notion that the effects of hormone therapy on CHD may vary according to when hormone therapy is started. Although the difference was not statistically significant, women who began hormone therapy close to the onset of menopause tended to have a reduced CHD risk, whereas women who started therapy later after menopause had an increased risk.

The issues just discussed are important and are being addressed in 2 prospective studies that are currently enrolling patients: the Kronos Early Estrogen Prevention Study (KEEPS) and the Early versus Late Intervention Trial with Estradiol (ELITE). KEEPS investigators are enrolling women aged 42-58 years who are within 3 years of their final menstrual period. The trial is anticipated to close in 2010. The aim of the ELITE trial is to compare women who underwent menopause within no more than 6 years with those who underwent menopause at least

10 years ago. Both trials are designed to evaluate different delivery systems, as well as doses lower than those assessed in the WHI and HERS.

A population based case-control study in the United Kingdom observed that transdermal hormone replacement therapy containing low-dose estrogen did not increase risk for stroke compared with no estrogen use. The risk for stroke was increased with use of high-dose transdermal estrogen and oral hormone replacement therapy (both high and low dose) when compared with no use.⁵⁴

Hormone Therapy and Breast Cancer

The potential link between hormone therapy and breast cancer has been controversial for many years. Observational studies, reported primarily in the 1970-1990s, tended to show an increased risk of breast cancer among women who use hormone therapy. The findings have typically shown that EPT carries a greater risk than does estrogen therapy. Some studies have not demonstrated an increased risk with estrogen therapy. The increased risk tends to be associated with long use (ie, >5 years).⁵⁵

Data from 51 epidemiologic studies revealed a significant increase in breast cancer with hormone therapy, with greatest increases observed with prolonged hormone therapy.⁵⁶ Women taking EPT or progestogen alone for more than 5 years had an RR of 1.15 compared with women who never received these treatments. Women who used 3 hormones for at least 5 years had an RR of 1.53. Among women taking estrogen alone, the risk of breast cancer increased only when duration of use was 5 years (RR, 1.34) or longer. Of interest, the increase in risk disappeared approximately 5 years after the cessation of hormone therapy.

Recent data from the Nurses' Health Study revealed an increase in risk of breast cancer (RR, 1.77) among women who used estrogen plus testosterone compared with women who were never given hormone therapy.⁵⁷ In addition, the risk of breast cancer rose among recipients of EPT (RR, 1.58). Patients taking estrogen alone had a relatively low risk (RR, 1.15), though it was still greater than that of nonusers.

Results from the WHI have confirmed an increased risk of breast cancer in EPT users. The EPT arm of the WHI was initially halted early secondary to an increased risk of total and invasive breast cancers in the women taking EPT compared with placebo after slightly more than 5 years of use. It was determined that there were 8 additional cases of breast cancer for every 10,000 women over 1 year. For the invasive breast cancers in the EPT group, they were larger, more likely to be node positive, and diagnosed at a significantly more advanced stage compared with placebo. Although the trend was for increased in-situ breast cancers in the EPT group, it was not statistically significant.⁴²

Women in the estrogen-alone arm of the WHI did not experience an increase in breast cancer after more than 7-year follow-up.⁴³ In fact, fewer breast cancers occurred in the women given estrogen therapy than in those given placebo. However, the difference was not statistically significant.

Mammographic breast density increases in women taking hormone therapy. Although the biologic importance of this finding has not been established, mammographic abnormalities require additional medical evaluation. Abnormal mammograms among women participating in the WHI were noted within the first year of treatment.⁴² Other investigators have also reported this finding. EPT slows the changes from a relatively dense pattern to the fatty pattern normally seen in women as they age. The effect of EPT is greater than that of estrogen therapy.⁵⁸ Transdermal EPT does not appear to increase breast density to the same degree that oral EPT does.⁵⁹

Of interest, the [Surveillance Epidemiology and End Results \(SEER\)](#) registries of the National Cancer Institute indicated a notable reduction of 6.7% in the incidence of breast cancer, particularly estrogen receptor–positive tumors, beginning in mid 2002. This timing corresponded to the WHI report of an increase in breast cancer with EPT; this report led to the discontinuation of hormone therapy in many women.⁶⁰ Some investigators suggested that this subsequent discontinuation of hormone therapy was what reduced the incidence of breast cancer.⁶¹ Others, including the [International Menopause Society](#), urge caution in linking these trends.

Hormone Therapy and Osteoporosis

Existing evidence largely supports the efficacy of hormone therapy in increasing bone mineral density and decreasing the risk of fracture. A meta-analysis of 22 randomized trials showed a significant reduction of 35% in nonvertebral fractures among women who began hormone therapy before the age of 60 years, with a possible attenuation of the benefit when hormone therapy is started after age 60 years.⁶² The WHI investigators also reported significant decreases in the fracture risk with both estrogen therapy and EPT.^{39,49} See [Table 5](#).

In fact, all of the hormone therapy preparations are indicated for the prevention of osteoporosis. Ultralow doses of oral or transdermal estrogen have also been shown to increase bone mineral density and decrease bone turnover in postmenopausal women^{63,64} and are indicated for osteoporosis prevention. Data about fractures are not yet available.

The stance adopted by the ACOG is that the use of hormone therapy for osteoporosis prevention or treatment needs to be individualized and needs to include the woman's need for treatment of vasomotor symptoms. Although other medications are available, such as bisphosphonates and selective estrogen receptor modulators, selected women with vasomotor symptoms may benefit from hormone therapy.⁶⁵

Hormone Therapy, Cognition, and Quality of Life

Limited data have linked the menopausal transition to a variety of mental health conditions, including depression, anxiety, and irritability, as well as to decreased cognitive function. The WHIMS substudy of the WHI was designed to address the effects of hormone therapy on cognitive function. In addition, issues related to health-related quality of life were analyzed in the WHI.

Cognition

Observational studies and several randomized controlled trials have provided limited evidence that hormone therapy positively affects cognition.⁶⁶ The WHIMS did not confirm these positive findings.^{67,68} No improvement in global cognitive function was observed in women using hormone therapy. In fact, the incidence of dementia and mild cognitive impairment increased among women taking hormone therapy. The increase was statistically significant only in the EPT group.

As with the findings for CVD, cognitive results differed in the WHI and other studies. As with CVD, some have hypothesized that hormone therapy may have been started at too late an age or too long after the onset of menopause to provide any benefit. Observations from both animal and human studies support this critical-period hypothesis.⁶⁹ Therefore, additional data are needed to elucidate the effect of the timing of hormone therapy on cognitive function.

Quality of life

Data about the effects of hormone therapy on health-related quality of life do not suggest a positive effect. The WHI data did indicate a significant improvement in sleep disturbance score with hormone therapy.^{70,71} However, no overall improvement was noted in health-related quality of life among women using hormone therapy.

Other Benefits and Risks of Hormone Therapy

Hormone therapy may also improve the incidence of colorectal cancer.^{39,72} [Table 5](#) also lists risks of hormone therapy, including stroke and venous thromboembolism.

Hormone Therapy After the WHI

Over the years, the number of prescriptions for hormone therapy has reflected scientific findings.

In the 1970s, the number of prescriptions increased to approximately 30 million per year. This practice was likely due to data describing the cardioprotective effects of hormone therapy.

In the 1980s, reports of increased rates of endometrial cancer with unopposed estrogen lead to a decrease in annual prescriptions to about 15 million. Then, the addition of progestogen for endometrial protection renewed interest in hormone therapy, and prescriptions again increased.

Between 1995 and 2002, annual prescriptions peaked at about 91 million. Termination of the estrogen-progestin arm of the WHI in July 2002 and release of HERS II data received considerable media attention and raised serious questions about the safety of hormone therapy in postmenopausal women. Many women stopped taking hormones and began to seek out alternative therapies. Prescriptions for hormone treatment immediately decreased. Of note, prescriptions for vaginal preparations did not change during this time.⁶⁰

In a 2010 published study by The Women's Health Initiative, estrogen plus progestin therapy appeared to increase the risk of breast cancer mortality and incidence when compared with placebo.⁷³

Current Recommendations for Hormone Therapy

In response to the findings from the WHI, many health organizations revised their recommendations regarding hormone therapy. Although hormone therapy should not be used for disease prevention, it is still appropriate as a treatment to relieve menopausal symptoms. The US Food and Drug Administration (FDA) required labeling information to include the following statement: "Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman."⁷⁴ The ACOG,⁶⁵ the NAMS,⁹ and the US Preventive Services Task Force⁷⁵ echoed these same recommendations.

Additional data on the health-related effects of hormone therapy in postmenopausal women are obviously needed. Although the WHI provided important information, only 1 hormonal preparation was evaluated. Many other preparations are available, including formulations with substantially lowered doses and formulations with different delivery systems. Until more data are available, following the current recommendations is prudent.

Bioidentical Hormone Therapy

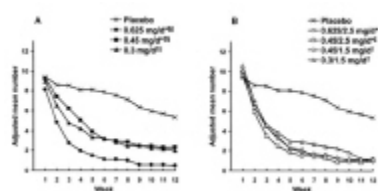
Bioidentical hormones are plant-derived compounds that have the same chemical and molecular structure as those of hormones produced by the human body. Pharmacists can custom prepare and package (compound) bioidentical hormones according to a physician's specifications. After results of the WHI were reported in 2002,

interest in bioidentical hormones increased because they have been promoted as a safer alternative to traditional hormone therapy, with the ability to tailor dosages of various estrogens. Although the existing studies on bioidentical hormones have not shown an increase in breast cancer, these studies have been too short in duration or methodologically flawed to show changes. These findings have unfortunately been interpreted as proof of safety rather than inconclusive. This may be misleading to the public.

Thus, the primary disadvantages of bioidentical hormone therapy are that these preparations have not undergone rigorous clinical testing for safety or efficacy and that they are not regulated by the FDA. Therefore, in addition to safety questions, quality assurance is a concern. Issues include the purity, potency, and quality of the products. Because these products are not FDA regulated, their labeling does not need to include the warning the FDA now requires for traditional hormone therapy.

No evidence suggests that bioidentical hormone therapy is safer than regulated hormone therapy. Professional medical societies (eg, ACOG⁷⁶, NAMS, The Endocrine Society⁷⁷) have published position statements regarding bioidentical hormones. These groups have expressed concerns regarding the lack of safety and efficacy data.

Multimedia



[\(Enlarge Image\)](#)

Media file 1: Mean daily number of hot flashes by week for various doses of conjugated estrogen (CEE) alone or combined with medroxyprogesterone acetate (MPA).(Utian, 2001) A, Placebo and CEE groups; B, Placebo and CEE-MPA groups.

Difference vs placebo was significant ($P < .05$) from weeks *2-12 or †3-12. ‡Difference between CEE 0.45 mg/d and CEE 0.45 mg/d with MPA 2.5 mg/d was significant ($P < .05$) at weeks 3, 4, 5, and 9. §Difference between CEE 0.625 vs 0.45 mg/d was significant ($P < .05$) from weeks 2-12. ||Difference between CEE 0.625 and 0.3 mg/d was significant ($P < .05$) at weeks 4, 5, 6, 9, 10, and 12.

Keywords

estrogen therapy, ET, estrogen in combination with a progestogen EPT, hormone replacement therapy, HRT, hormonal replacement therapy, hormone therapy, HT, hormonal therapy, progesterone, progestin, progestogen, estrone, estriol, estradiol, 17beta-estradiol, menopause, postmenopause, postmenopausal, perimenopause, perimenopausal, menopausal transition, hot flashes, hot flushes, night sweats, vaginal dryness, medroxyprogesterone acetate, MPA, Heart and Estrogen/Progestin Replacement Study, HERS, Kronos Early Estrogen Prevention Study, KEEPS, Early versus Late Intervention Trial with Estradiol, ELITE, Women's Health Initiative, WHI, bioidentical hormones