Centro Médico
Instituto Palacios
Salud de la Mujer

USO DE ESTRADIOL TRASDERMICO Y DE PROGESTERONA MICRONIZADA

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GINECOLOGÍA | INVESTIGACIÓN | FORMACIÓN

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Desde el año 1990, llevamos a cabo un proyecto clínico-asistencial con el objetivo de conseguir una mejor calidad de vida de la mujer

La promoción de la salud, el envejecimiento saludable y la prevención y tratamiento de la enfermedades de las mujeres son la base del centro.

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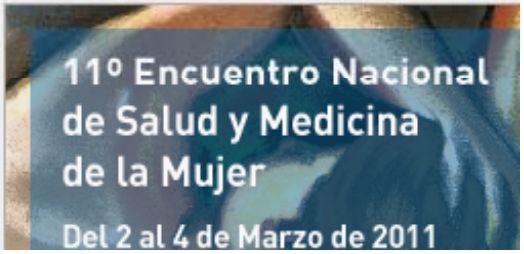


TRH 2011

- **TH**
  - **-Ventana de oportunidad**
  - **-Baja y ultra-baja dosis de estrógenos.**
  - **-Gestágenos con valor añadido**
  - **-Añadir un andrógeno**
- **PAPEL ESPECIAL DE LA RUTA PERCUTANEA.**
- **DATOS SOBRE TRH EN EL 2011**

TRH: El nuevo paradigma

FDA

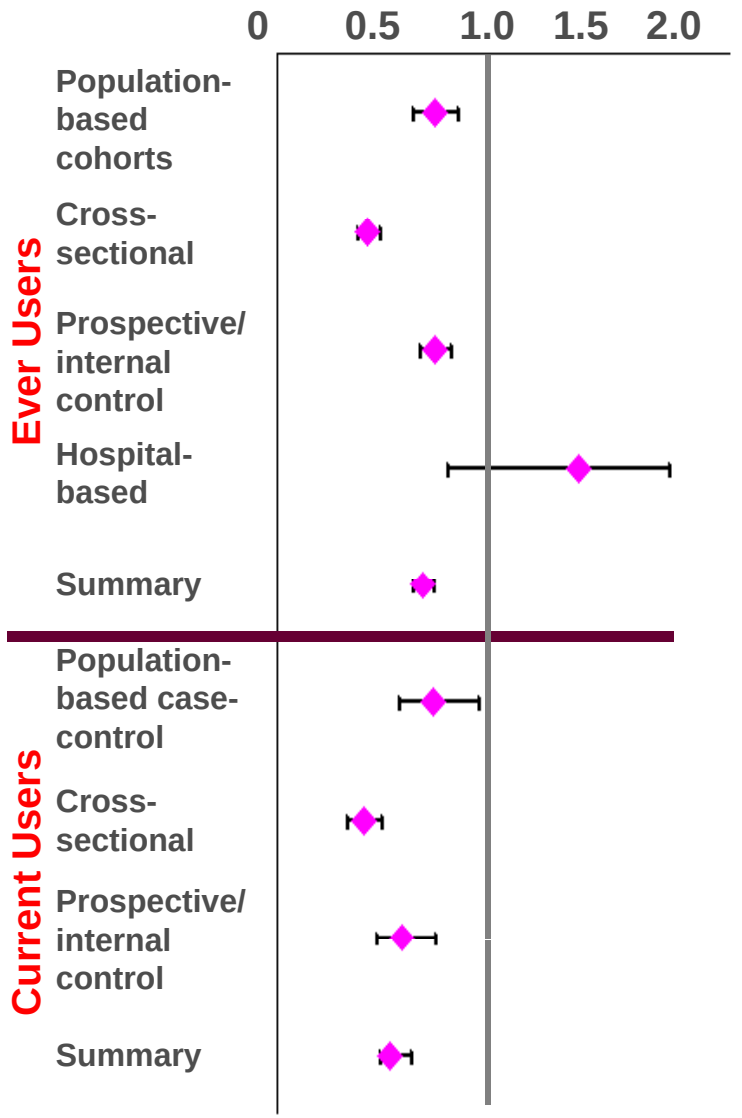
WHI
Million Women Study

Reduciendo la dosis
Acortando la duración
Mujer sintomática

Dec. 2003

HT and CHD: Meta-Analysis
of Observational Studies

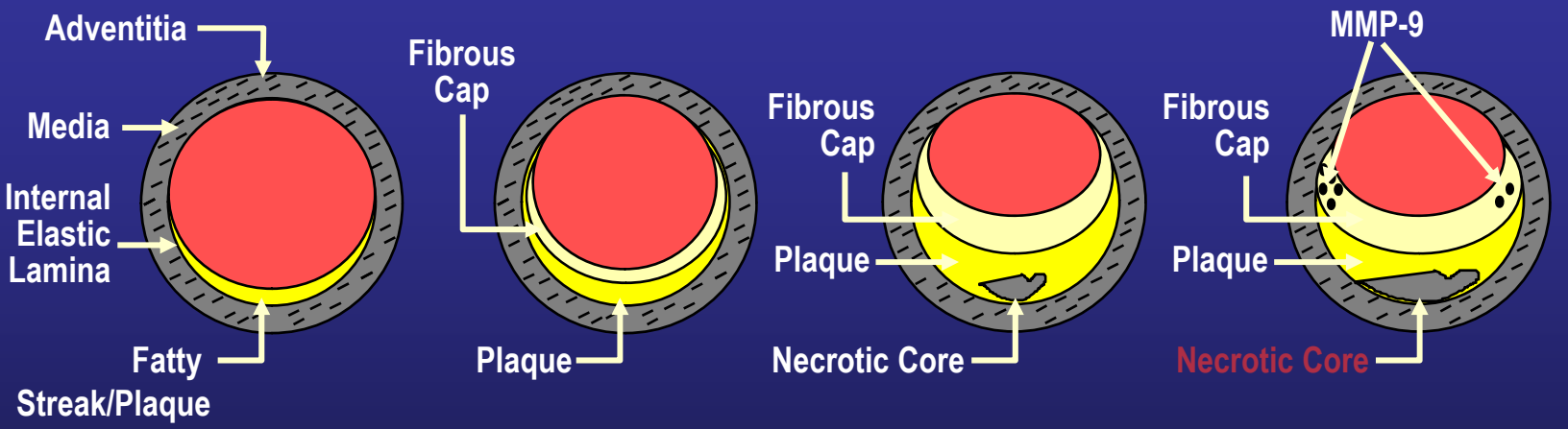
Based on more than 40 observational studies of HT and CHD, the summary relative risks for CHD were 40-50% lower among current or ever users of HT compared to never users (p<0.001).



DIFERENCIAS ENTRE ESTUDIOS OBSERVACIONALES Y EL WHI

	WHI	Observational Studies
Edad de iniciación de la TH	63 años	52 años
Tiempo desde la menopausia	12 años	1-2 años
Síntomas vasomotores	General –	General+
IMC	28-30	24-25
Uso de TH	Corto	Largo
Formulaciones de TH	CEE+MPA	Diversas

Relación de los años desde la menopausia con la progresión de arterioesclerosis en el WHI



Years Postmenopause	<5	5 to <10	10 to <15	≥15
% of WHI Enrollees	17%	19%	21%	43%

Mortalidad total asociada con la TRH en mujeres jóvenes y mayores: Meta-análisis de 30 estudios controlados randomizados

HRT versus Control	OR (95% CI)
All Ages	0.98 (0.87-1.18)
>60 years (Mean age 66 years)	1.03 (0.91-1.16)
<60 years (Mean age 54 years)	0.61 (0.39-0.95)

Salpeter S et al. *J Gen Intern Med* 2004;19:791-804

Absolute Excess Risks (cases per 10,000 pys) by Age in the Combined Trials (E+P and E-Alone) of the WHI

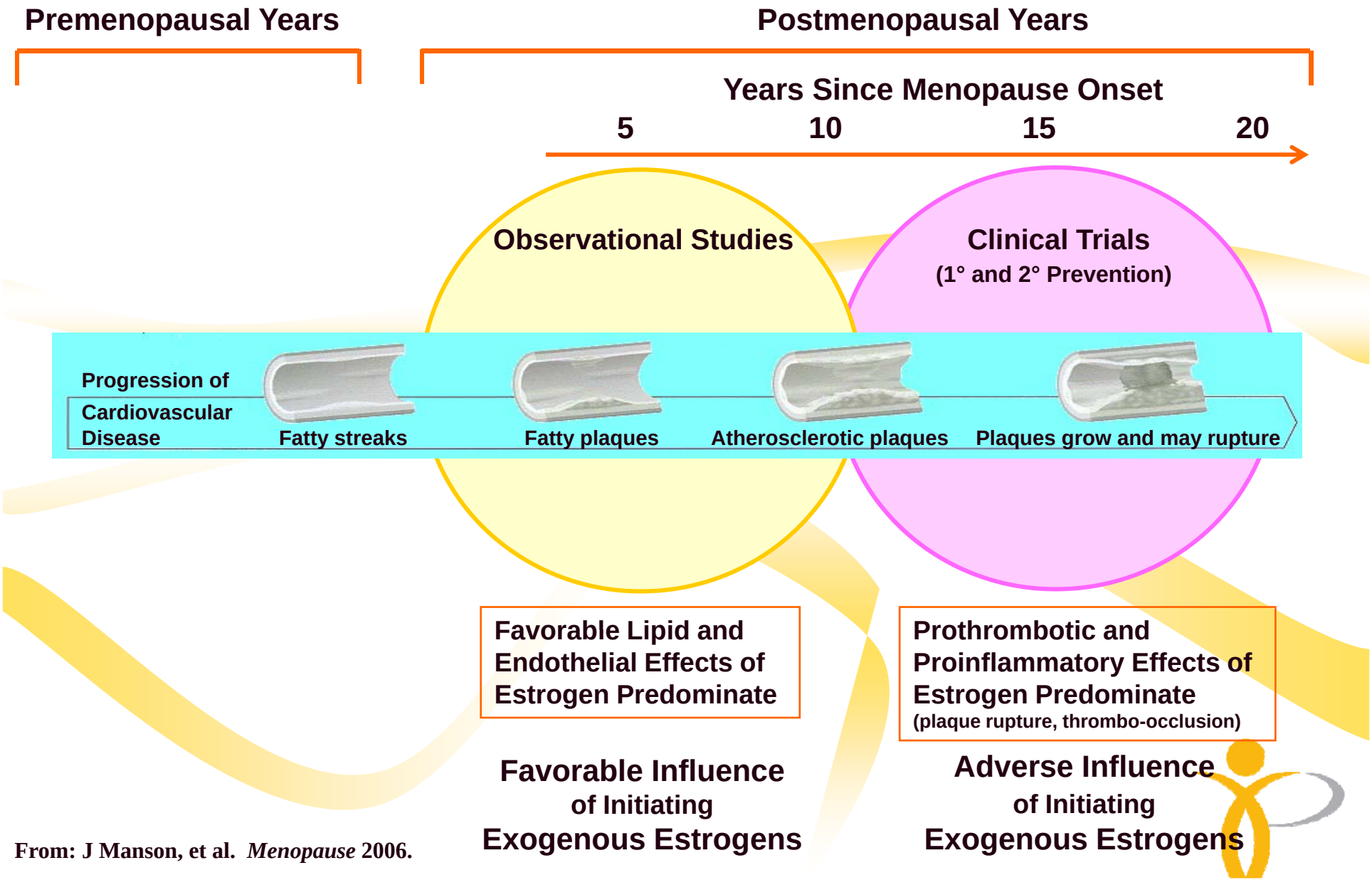
Outcome	Age (years)		
	50-59	60-69	70-79
CHD	-2	-1	+19*
Total mortality	-10	-4	+16*
Global index†	-4	+15	+43

* P=0.03 compared with age 50-59 years or <10 years since menopause

† Global index is a composite outcome of CHD, stroke, pul embolism, breast ca, colorectal ca, endometrial ca, hip fracture and mortality

Source: Rossouw JE, Prentice RL, Manson JE, et al. *JAMA* 2007.

Timing of Hormone Therapy Initiation in Relation to Stage of Atherosclerosis: Observational Studies vs Clinical Trials



From: J Manson, et al. *Menopause* 2006.

Different mechanisms for benefit and risk of coronary heart disease and stroke in early postmenopausal women: a hypothetical explanation.

Menopause. 2011 Feb;18(2):237-40.
Lobo RA, Clarkson TB.

Abstract

In younger postmenopausal women, estrogen is thought to be protective against coronary heart disease. The mechanism for this effect is likely to be an inhibition of the development of atherosclerosis. However, in older postmenopausal women with established atherosclerosis, the initiation of estrogen therapy may cause coronary artery plaque instability and rupture, resulting in coronary thrombosis and myocardial infarction. Compared with these findings of coronary disease prevention in younger women, estrogen therapy has been linked to an increased risk of ischemic stroke in both younger and older postmenopausal women, although the risk is small and the event rate in younger women is considered to be rare. Here, we provide an argument that the mechanism for stroke risk in younger women is not based on atherosclerotic disease, as occurs in older women for both coronary disease and stroke, but is related to thrombosis. **Susceptibility for stroke is increased in women, and various factors leading to thrombosis may explain this risk. This notion is supported by data that estrogen regimens that decrease the risk of venous thrombosis (lower oral doses and transdermal therapy) may not be associated with an increase in ischemic stroke risk.**

Timing and duration of menopausal hormone treatment may affect cardiovascular outcomes.

Am J Med. 2011 Mar;124(3):199-205.

Harman SM, Vittinghoff E, Brinton EA, Budoff MJ, Cedars MI, Lobo RA, Merriam GR, Miller VM, Naftolin F, Pal L, Santoro N, Taylor HS, Black DM.

Abstract

Largely on the basis of the first publication of findings of net harm with menopausal hormone treatment in the Women's Health Initiative (WHI) hormone trials, current Food and Drug Administration recommendations limit menopausal hormone treatment to the "…shortest duration consistent with treatment goals…," with goals generally taken to mean relief of menopausal symptoms and maximal duration as approximately 5 years. The WHI finding of net harm was due largely to the absence of beneficial effects on coronary heart disease incidence rates. Published analyses of WHI data by age or time since menopause find that excess coronary heart disease risk with menopausal hormone treatment is confined to more remotely menopausal or older women, with younger women showing nonsignificant trends toward benefit (the "timing hypothesis"). Moreover, a recently published reexamination of data from the WHI Estrogen plus Progestin trial suggests that reduced coronary heart disease risk may appear only after 5 to 6 years of treatment. Consistent with this finding, risk ratios for coronary heart disease were calculated as 1.08 (95% confidence interval, 0.86-1.36) in years 1 to 6 and as 0.46 (confidence interval, 0.28-0.78) in years 7 to 8+ in the WHI Estrogen Alone trial. Previous studies also support the beneficial effects of menopausal hormone treatment after prolonged exposure. Thus, current analyses do not support a generalized recommendation for short duration of menopausal hormone treatment. Rather, **they suggest that current Food and Drug Administration practice guidelines should be reconsidered to allow individualized care based on risk:benefit considerations. New research is urgently needed evaluating influences of timing, duration, dose, route of administration, and agents on menopausal hormone treatment-related risks and benefits to better understand how to optimize recommendations for individual patients.**

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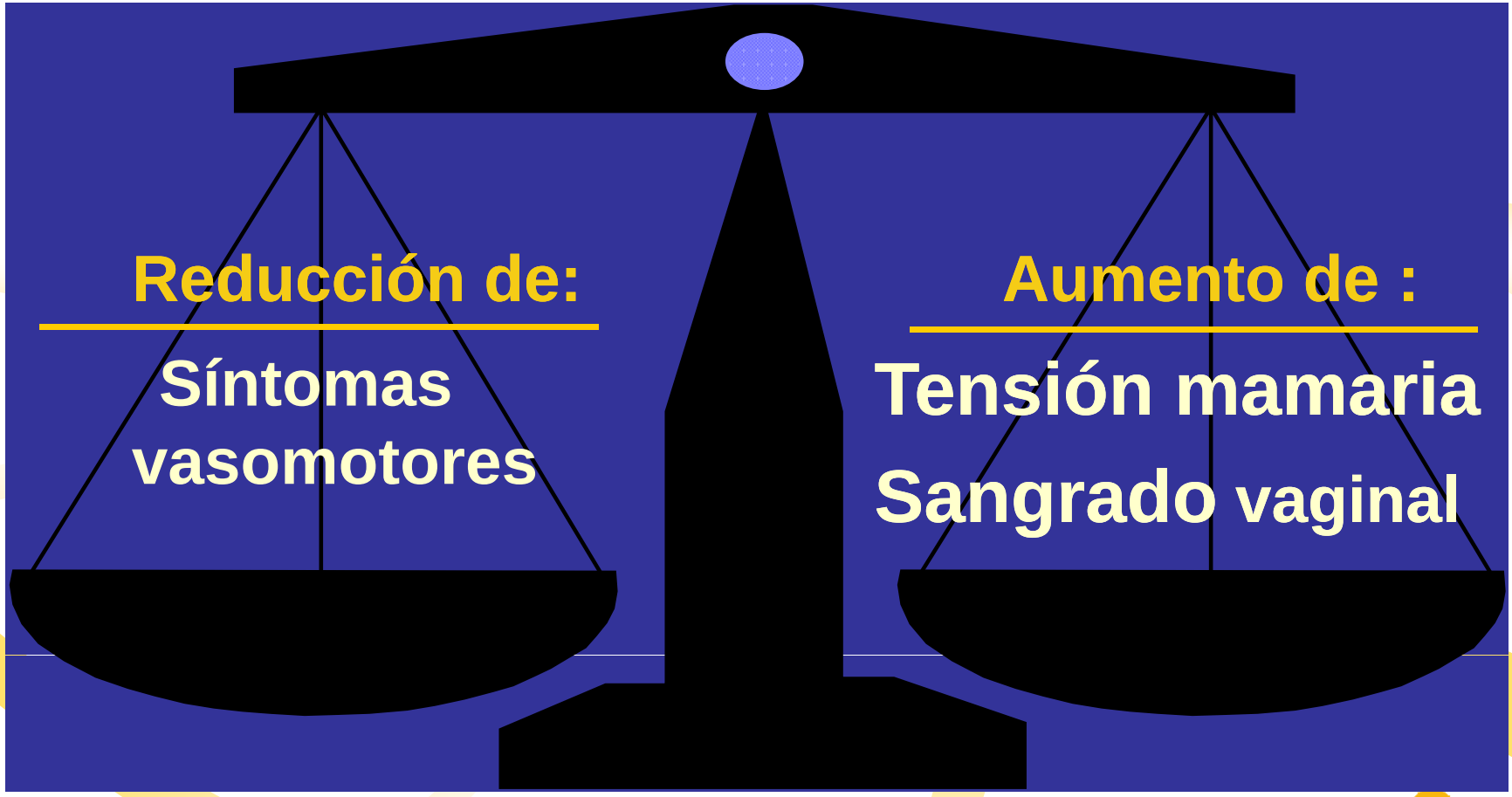
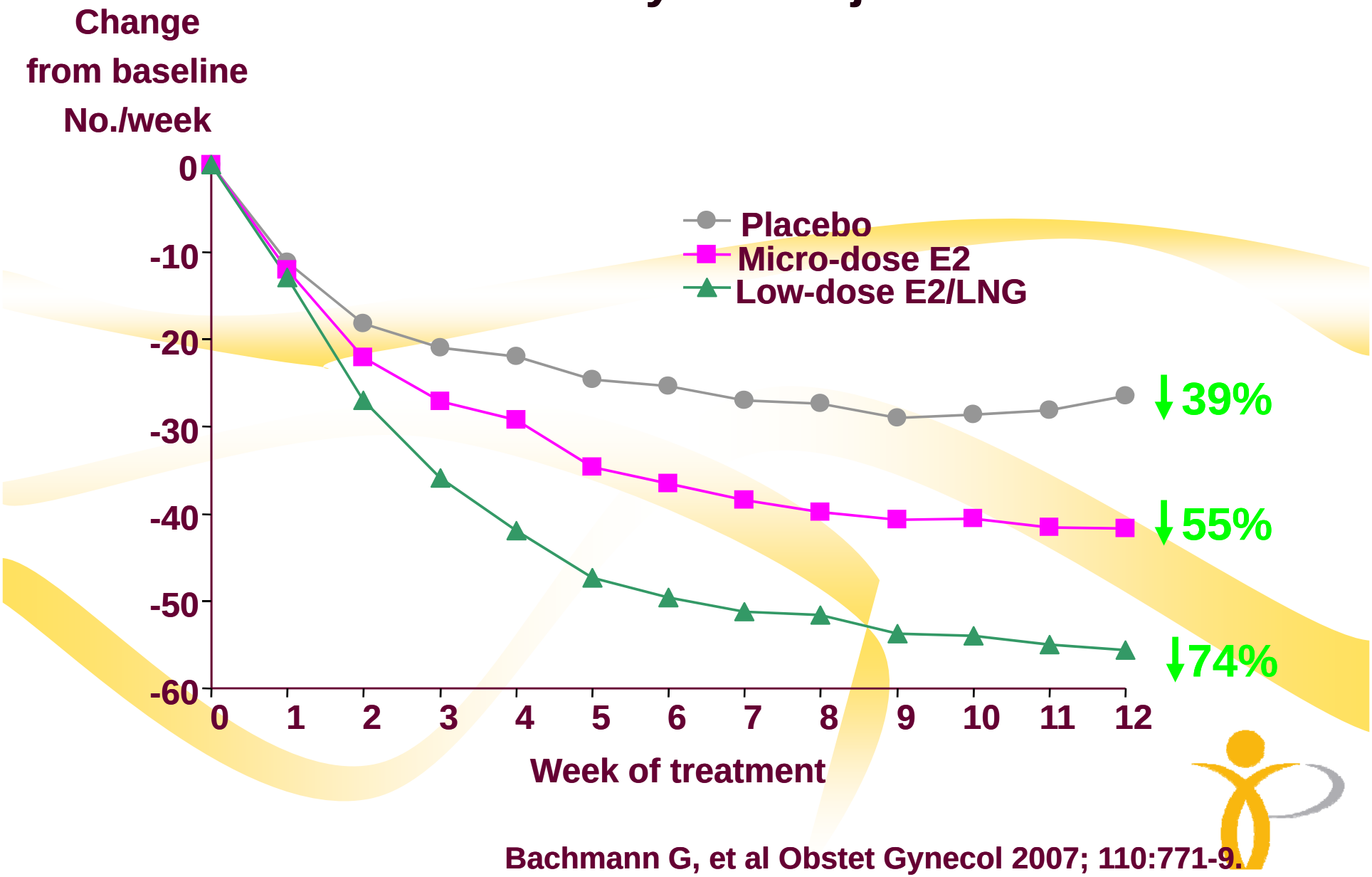
Balance entre desaparición de unos síntomas-aparición de otros

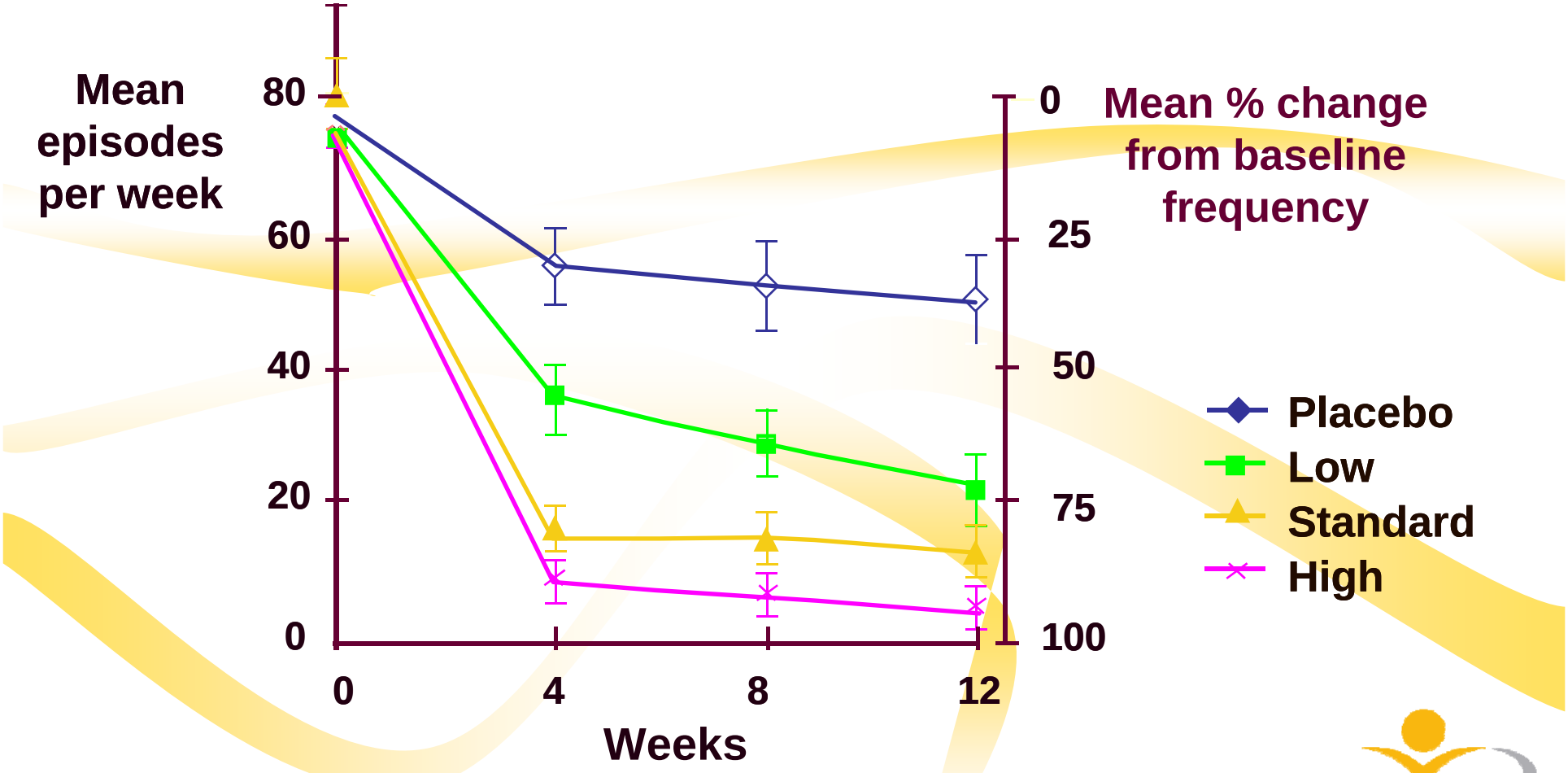


Desaparición de síntomas vasomotores entre baja dosis y ultrabaja



Bachmann G, et al Obstet Gynecol 2007; 110:771-9.

Respuesta a las diferentes dosis de estrógenos



Ettinger B. Am J Med 2005;118:74S-78S

TRH 2011

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Progestágenos: efectos en los receptores

(progesterone derivatives)

Progestogen	EST	A-E	AND	A-A	GLU	A-M
progesterone	-	+	-	(+)	(+)	+
medroxyprogesterone	-	+	(+)	-	+	-
dydrogesterone	-	+	-	-	-	(+)
chlormadinone acetate	-	+	-	+	+	-
medrogestone	-	+	-	(+)	-	-
cyproterone acetate	-	+	-	+	+	-
drospirenone	-	+	-	+	-	+

WHI: Informe sobre el Cáncer de Mama E-Solo actualizado

Overall: HR=0.80; CI=0.62-1.04

Adherent Pts: HR=0.67 CI=0.47-0.97

No effect on in-situ disease.
Only ductal cancers and in women with no prior hormone therapy.

More follow-up mammograms/biopsies/aspirations.

JAMA 2006;295:1647

French E3N Cohort Study

SPEROFF

54,548 women; 0.1-10.6 years follow-up
55% gels; 45% patches

E alone	30 cases	1.1 (0.8-1.6)
E/Progesterone	55 cases	0.9 (0.7-1.2)
E/Progestins	268 cases	1.4 (1.2-1.7)

Int J Cancer 2005;114:448

Breast cancer risk in relation to the interval between menopause and starting hormone therapy.

J Natl Cancer Inst. 2011 Feb 16;103(4):296-305.

Beral V, Reeves G, Bull D, Green J; Million Women Study Collaborators.
Collaborators

Abstract

BACKGROUND: Although breast cancer risk is greater in users of estrogen-progestin than estrogen-only formulations of menopausal hormonal therapy, reports on their effects have been somewhat inconsistent. We investigated whether the timing of these therapies affected breast cancer incidence.

METHODS: A total of 1,129,025 postmenopausal UK women provided prospective information on hormonal therapy use and other factors relevant for breast cancer risk. We used Cox regression to estimate adjusted relative risks (RRs) of breast cancer in hormonal therapy users vs never users and calculated standardized incidence rates. All statistical tests were two-sided.

RESULTS: During 4.05 million woman-years of follow-up, 15,759 incident breast cancers occurred, with 7107 in current users of hormonal therapy. Breast cancer incidence was increased in current users of hormonal therapy, returning to that of never users a few years after use had ceased. The relative risks for breast cancer in current users were greater if hormonal therapy was begun before or soon after menopause than after a longer gap (P(heterogeneity) < .001, for both estrogen-only and estrogen-progestin formulations). Among current users of estrogen-only formulations, there was little or no increase in risk if use began 5 years or more after menopause (RR = 1.05, 95% confidence interval [CI] = 0.89 to 1.24), but risk was statistically significantly increased if use began before or less than 5 years after menopause (RR = 1.43, 95% CI = 1.35 to 1.51). A similar pattern was observed among current users of estrogen-progestin formulations (RR = 1.53, 95% CI = 1.38 to 1.70, and RR = 2.04, 95% CI = 1.95 to 2.14, respectively). At 50-59 years of age, annual standardized incidence rates for breast cancer were 0.30% (95% CI = 0.29% to 0.31%) among never users of hormone therapy and 0.43% (95% CI = 0.42% to 0.45%) and 0.61% (95% CI = 0.59% to 0.64%), respectively, among current users of estrogen-only and estrogen-progestin formulations who began use less than 5 years after menopause.

CONCLUSIONS: There was substantial heterogeneity in breast cancer risk among current users of hormonal therapy. Risks were greater among users of estrogen-progestin than estrogen-only formulations and if hormonal therapy started at around the time of menopause than later.

Impact of HT on DVT by route of administration and type of progestin

	Cases (n=259)	Controls (n=603)	Matched OR (95% CI) Crude	Adjustment 1	Adjustment 2
Nonuse	146	384	1	1	1
Oral estrogen use	45	39	3.6 (1.5–8.8)	4.0 (1.6–10.1)	4.2 (1.5–11.6)
Transdermal estrogen use	67	180	0.8 (0.4–1.6)	0.8 (0.4–1.8)	0.9 (0.4–2.1)
No progestogens	14	40	...	...	...
Micronized progesterone	19	63	1.0 (0.4–2.3)	0.9 (0.4–2.2)	0.7 (0.3–1.9)
Pregnane derivatives	39	79	1.0 (0.4–2.3)	0.9 (0.4–2.2)	0.9 (0.4–2.3)
Norpregnane derivatives	40*	37†	3.8 (1.6–8.7)	4.0 (1.7–9.4)	3.9 (1.5–10.0)

Users of oral estrogen combined with nortestosterone derivatives (12 cases, 7 controls) were excluded (OR, 6.7; 95% CI, 2.1 to 21.9 vs nonusers). Estrogen-by-progestogen interaction terms were not significant. Adjustment 1: adjustment for obesity status, familial history of VTE, and history of varicose veins. Adjustment 2: adjustment for obesity status, familial history of VTE, history of varicose veins, education, age at menopause, hysterectomy, and cigarette smoking.

*Twenty-two cases received nomegestrol acetate, and 18 cases received promogestone.

†Nineteen controls received nomegestrol acetate, and 18 controls received promogestone.

Cannonico et al. Circulation 2007

Increased thrombin generation among postmenopausal women using hormone therapy: importance of the route of estrogen administration and progestogens.

Menopause. 2011 Aug;18(8):873-9.

Scarabin PY, Hemker HC, Clément C, Soisson V, Alhenc-Gelas M.

Abstract

OBJECTIVE: Increased thrombin generation has emerged as a new surrogate marker of venous thromboembolism. Using calibrated automated thrombography, we tested the influence of the route of estrogen administration and progestogens on thrombin generation among postmenopausal women using hormone therapy.

METHODS: Baseline thrombin generation, together with clotting factors and inhibitors, was determined in plasma from 115 healthy postmenopausal women. Women were classified by the use of hormone therapy into three groups: nonusers (n = 38), users of oral estrogens (n = 38), and users of transdermal estrogens (n = 39).

RESULTS: Oral estrogens dose dependently increased thrombin generation. Thrombin generation was increased among users of transdermal estrogens combined with progestins but was similar to nonusers among women using transdermal estrogens plus progesterone. Prothrombin was the main determinant of thrombin generation and explained a part of these differences. However, single clotting factors and inhibitors contributed little to the hormone-related changes in thrombin generation.

CONCLUSIONS: Increased thrombin generation can be detected in women using hormone therapy, but this hypercoagulable phenotype depends both on the route of estrogen administration and the type of progestogens. These findings are consistent with current data on the risk of venous thromboembolism related to hormone therapy.

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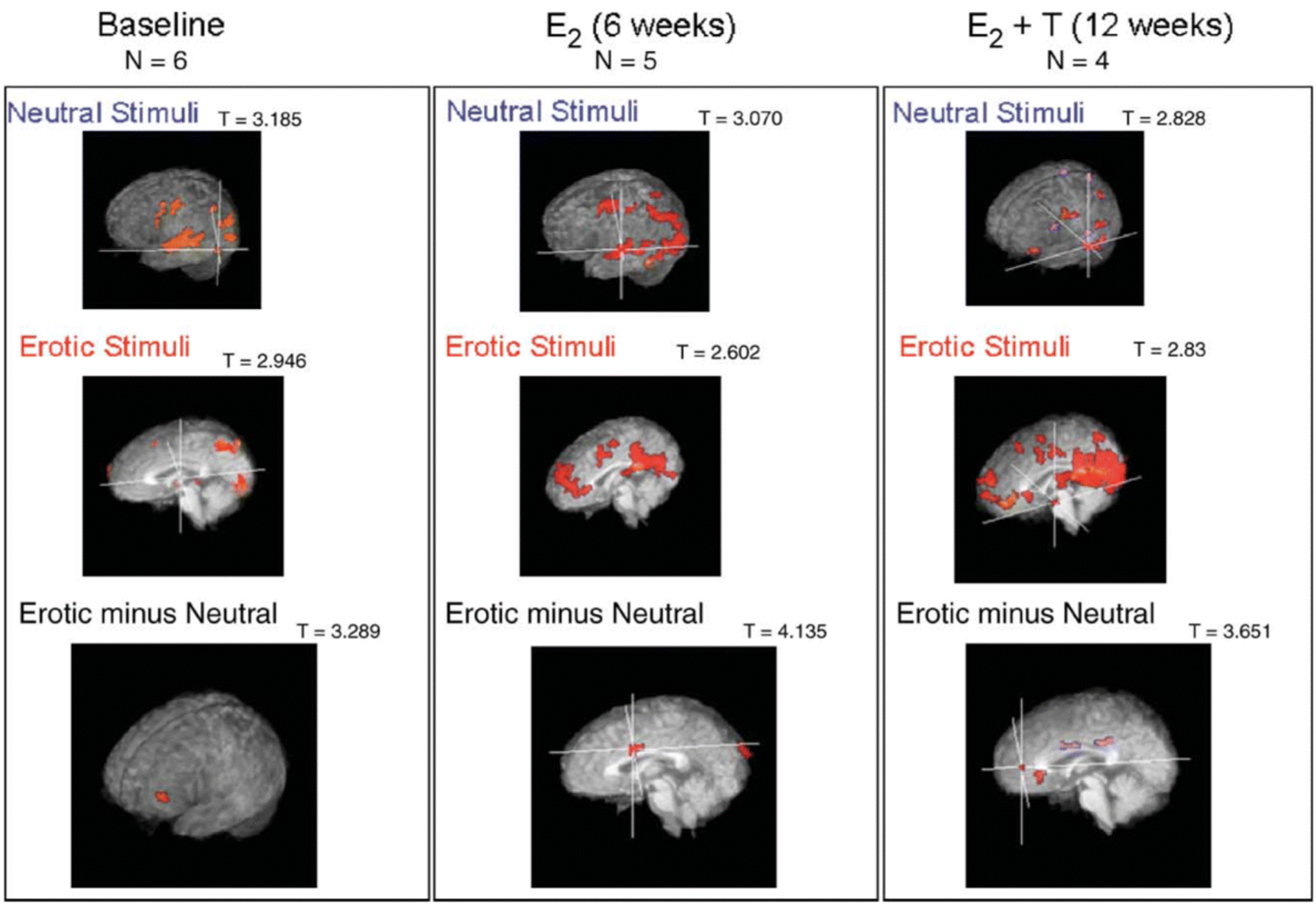
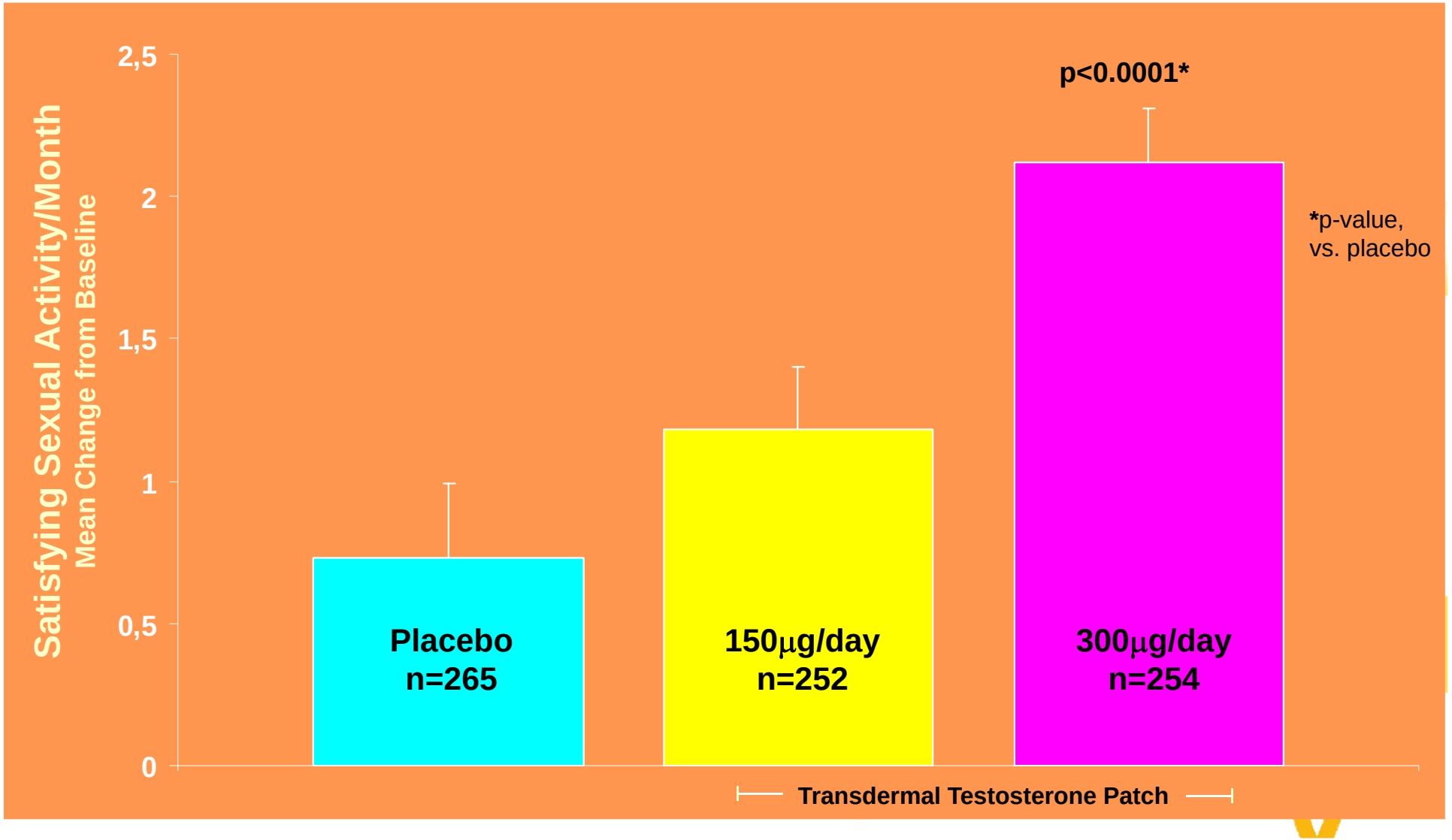
EFFECTS OF E/TE ON FUNCTIONAL MRI



APHRODITE (Transdermal Testosterone Patch Only) Increased Total Satisfying Sexual Activity at 24 Weeks



FUTURE RECOMENDATIONS

1. Double-blind, randomized controlled studies
2. Research should measure the number of women who improve, do not improve, get worse...
3. Testosterone benefits on wellbeing, cognition ...
4. Adverse effects, hematocrit, coagulation factors...
5. Long-term complications
6. Testosterone alone vs. T. plus E.
7. The effects of different progestin with T. plus E.
8. Target population
9. Duration of treatment

Somboonporn W. et al. The Cochrone Library 2007, Issue 2

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PERCUTANEO/TRANS DERMICO VS ORAL

¿EXISTE ALGUNA DIFERENCIA?

LA PRINCIPAL DIFERENCIA FARMACOLOGICA

ORAL 4-5 VECES MAS NIVELES HEPATICOS

PERCUTANEO:
estrona:estradiol = 1
Oral E1:E2 = 5

LA PREGUNTA

¿ EL PRIMER PASO HEPATICO, TIENE REPERCUSIONES CLÍNICAS?

CONCEPTOS CLAROS

LA VIA ORAL Y LAS VIAS DERMICAS TIENEN EL MISMO PAPEL SOBRE SINTOMAS Y HUESO

Ann Int Med 117:1, 1992
Osteoporosis Int 4:341, 1994
Am J Ob Gyn 181:71, 1999
J Bone Min Res 22:1791, 2007

PUNTOS CONTROVERTIDOS

ENFERMEDAD CARDIOVASCULAR
METABOLISMO DE CARBOHIDRATOS
CANCER

FACTORES DE COAGULACION

ORAL, AUMENTA
Factor VII, Prothrombin 1+2 fragment,
REDUCE TFPI

Percutaneo: disminuye Factor VII, no efecto sobre TFPI

Ambos: Reducen tPA, PAI-1, Fibrinogeno, Antithrombina III, Proteina S

Thromb Haemost 85:619,2001
Maturitas 50:344,2005
Maturitas 53:267 2006
Gynecol Obstet Invest 64:61, 2007
Thromb Haemost 97:558, 2007
Gynecol Obstet Invest 65:47, 2008

¿Qué significa?

Oral: hay un aumento de la coagulación y de la fibrinolisis.

Dérmicos: Probablemente sin efecto.

Actividad de la proteina C

Oral: Aumento de 103% ;
Dérmicos Aumento de 27%

Arterioscl Thromb Vasc Biol 23:1116, 2003

Oral aumenta; Dérmicos no afectan

Arterioscl Thromb Vasc Biol 23:1671, 2003
Thromb Haemost 86:550, 2001

Estudio caso-control de TEV

ESTHER- 235 casos

	Casos	Controles	Odds Ratio
Oral	51	44	4.3 (2.6-7.2)
TD /Perc	60	169	1.2 (0.8-1.7)

Circulation 112:3495, 2005

J Thromb Haemost 4:1259, 2006

Mujer con hipertrigliceridemia

Dérmicos disminuyen el nivel un 11%

Gynecol Endocrinol 18:233,2004

EL SISTEMA RENINA ANGIOTENSINA

Am J Hypertens 19:744, 2006

ESTROGENOS ORALES LA INCREMENTAN

ESTROGENOS DERMICOS NO LA INCREMENTAN

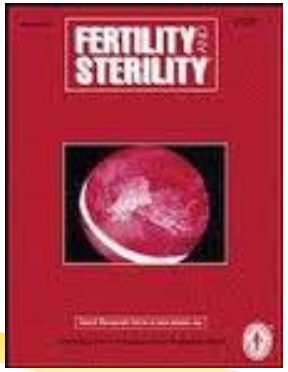
Marcadores del cancer de mama:

Oral- disminuye IGF-I
aumenta SHBG

Dérmico- no cambios

Clin Cancer Res 10:4389,2004

Effects of percutaneous estradiol-oral progesterone versus oral conjugated equine estrogens-medroxyprogesterone acetate on breast cell proliferation and bcl-2 protein in healthy women.



Fertil Steril. 2011 Mar 1;95(3):1188-91. Epub 2010 Nov 10.
Murkes D, Conner P, Leifland K, Tani E, Beliard A, Lundström E, Söderqvist G.
Source

Abstract

In a prospective, randomized clinical study 77 women were assigned randomly to receive sequential hormone therapy with either conventional oral conjugated equine estrogens (0.625 mg) with the addition on 14 of the 28 days of oral medroxyprogesterone acetate (5 mg) or natural E(2) gel (1.5 mg) with oral micronized P (200 mg) on 14 of the 28 days of each cycle. Because oral conjugated equine estrogens-medroxyprogesterone acetate induced a highly significant increase in breast cell proliferation in contrast to percutaneous E(2)-oral P with a difference between therapies approaching significance, the former therapy has a marked impact on the breast whereas natural percutaneous E(2)-oral micronized P has not.

Ventajas de las vías dérmicas

Efecto de los estrogenos Orales :

SHBG 132% Free T -33%

Efecto de los estrogenos dermicos :

SHBG 12% Free T 1%

Menopause 14:985, 2007

Resumen

Factores	Oral	Dérmico
	↓ ↓	↓
HDL	↑↑	↑
HDL proinflamatoria	↑	↓
Triglicéridos	↑	↓
Factor VII	NS	↓
Prothrombin F1+2a	↑	NS or ↓
VTE	↑	NS
CRP	↑	NS
SAA	↑	↓
PS sistolica	↑	↓

CONCLUSIONES

1. NECESIDAD DE ESTUDIOS SOBRE EVENTOS CLINICOS.

CONCLUSIONES

LA TERAPIA PERCUTANEA

1. Una opción para todas las pacientes.
2. Indicada para pacientes con alto riesgo de trombosis venosa.
3. Indicada para la hipertriclicerinemia.
4. Indicada para la obesidad y síndrome metabólico.
5. Indicada probablemente para fumadoras e hipertensas.

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Timing of hormone therapy and dementia: the critical window theory revisited.

Ann Neurol. 2011 Jan;69(1):163-9.

Whitmer RA, Quesenberry CP, Zhou J, Yaffe K.

Abstract

OBJECTIVE: Although previous research has shown that initiation of postmenopausal estrogen hormone therapy (HT) in late life increases risk of dementia, animal studies and some observational studies have suggested that midlife use of HT may be beneficial; however, this has not been rigorously investigated in large population-based studies. Our objective was to compare HT use in midlife with that in late life on risk of dementia among 5,504 postmenopausal female members of an integrated healthcare delivery system.

METHODS: HT use was determined at midlife (mean age, 48.7 years) from a survey in 1964 and in late life (mean age, 76 years) using pharmacy databases from 1994 to 1998. Risk of dementia diagnosis was evaluated with inpatient and outpatient diagnoses made in Neurology, Neuropsychology, and Internal Medicine from 1999 to 2008. Cox proportional hazard models were used to examine effects of HT use at different times on dementia risk with adjustment for age, education, race, body mass index, number of children, and comorbidities.

RESULTS: A total of 1,524 women (27%) were diagnosed with dementia during the follow-up period. Compared to women never on HT, those taking HT only at midlife had a 26% decreased risk (multivariate adjusted hazards ratio [aHR], 0.74; 95% confidence interval [CI], 0.58-0.94), whereas those taking HT only in late life had a 48% increased risk (aHR, 1.48; 95% CI, 1.10-1.98), and women taking HT at both mid and late life had a similar risk of dementia (aHR, 1.02; 95% CI, 0.78-1.34).

INTERPRETATION: These findings suggest that use of HT in midlife only may protect against cognitive impairment, whereas HT initiation in late life could have deleterious effects.

National Osteoporosis Society's Position statement on hormone replacement therapy in the prevention and treatment of osteoporosis.

Menopause Int. 2011 Jun;17(2):63-5.
Bowring CE, Francis RM.

Abstract

Hormone replacement therapy (HRT) has been shown to increase bone density, reduce the risk of fracture and can successfully relieve menopausal symptoms. From a time when HRT was the major therapeutic option for the management of osteoporosis, women and their clinicians now have a range of treatments available. Following the publication of the Women's Health Initiative (WHI) and the Million Women Study highlighting potential side-effects, such as breast cancer, heart disease and stroke, many doctors and women are now reluctant to use HRT. The National Osteoporosis Society felt that the role of HRT in the management of osteoporosis needed to be clarified. Using the Charity's expert clinical and scientific advisers, and through public consultation with members and key stakeholders, a Position Statement has been published. We conclude that HRT has a role to play in the management of osteoporosis in postmenopausal women below the age of 60 years. The key recommendations of the Position Statement are presented in this paper.

Risk of osteoporotic fractures after discontinuation of menopausal hormone therapy: results from the E3N cohort.

Am J Epidemiol. 2011 Jul 1;174(1):12-21.

Engel P, Fabre A, Fournier A, Mesrine S, Boutron-Ruault MC, Clavel-Chapelon F.

Abstract

While current use of menopausal hormone therapy (MHT) reduces the risk of osteoporotic fractures, epidemiologic studies suggest that protection wears off rapidly after discontinuation of treatment. The authors identified 5,589 first osteoporotic fractures (2,235 major osteoporotic fractures) among 70,182 postmenopausal women from the French E3N cohort (1992-2008) and used Cox multivariate proportional hazards regression models to estimate hazard ratios. Persistence of protection against major osteoporotic fractures after MHT discontinuation was only observed when MHT had been used for at least 5 years, with a slightly more important decrease within the 5 years after discontinuation (compared with never use of MHT, hazard ratio = 0.68, 95% confidence interval: 0.50, 0.92) than beyond 5 years (hazard ratio = 0.83, 95% confidence interval: 0.69, 0.99); the P value for homogeneity between the 2 estimates was not significant. Oral estrogen use and transdermal estrogen use conveyed similar estimates in past users. Among current users, the authors confirmed a protective effect of MHT against risk of osteoporotic fractures. **These findings, which relied on a number of MHT combinations, suggested that such therapies should be used for 5 years or more for reducing risk of fracture after treatment discontinuation.**

Hormone replacement therapy in gynecologic cancer survivors: why not?

Gynecol Oncol. 2011 Aug;122(2):447-54. Epub 2011 Apr 6.

Ibeanu O, Modesitt SC, Ducie J, von Gruenigen V, Agueh M, Fader AN.

Abstract

PURPOSE: As a result of treatment, many women with gynecologic malignancies will go through menopause and display climacteric symptoms at an earlier age than occurs naturally. Iatrogenic menopause may adversely affect quality of life and health outcomes in young female cancer survivors. Hormone replacement therapy (HRT) has often been withheld from women with gynecologic cancer because of concern that it might increase the risk of relapse or the development of new primary cancers. The purpose of this review was to examine the published literature on menopause management in gynecologic cancer survivors and highlight the risks and benefits of conventional and alternative HRT in this population.

METHODS: A comprehensive literature search of English language studies on menopause management in gynecologic cancer survivors and women with a hereditary predisposition to a gynecologic malignancy was performed in MEDLINE databases through December 2010.

RESULTS: Both our review and a 2008 Cochrane review of randomized trials on the effects of long-term HRT demonstrate that for menopausal women in their 40s or 50s with and without gynecologic cancer, the absolute risks of estrogen-only HRT are low. Several prospective observational studies and randomized trials on HRT use in women with a genetic predisposition for or development of a gynecologic malignancy suggest benefits in quality of life with no proven adverse oncologic effects as a result of short-term HRT use.

CONCLUSION: In select women, it is reasonable to discuss and offer conventional HRT for the amelioration of menopausal symptoms and to improve quality of life. HRT does not appear to increase the risk of gynecologic cancer recurrences; however, this conclusion was largely based on observational data and smaller prospective studies.