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ESGO | European Network of Gynaecological Cancer Advocacy Groups

Patient Advocacy Seminar

Oct 28–30, 2022, Berlin, Germany

Hormonal substitution in gynaecological cancer treatment

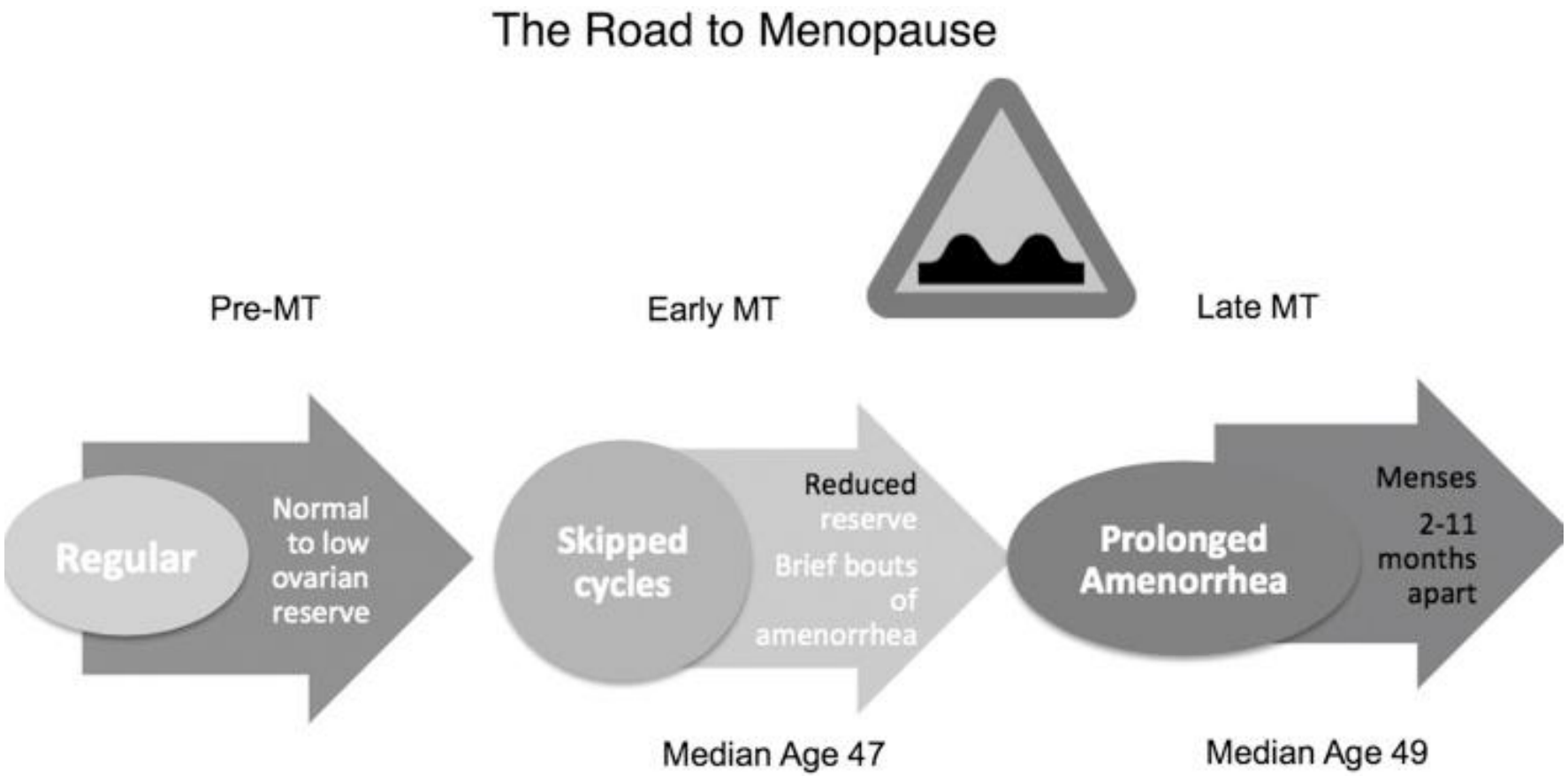
Dr. Desislava Dimitrova

Department of Gynecology with Center for Oncological Surgery, Charité-University Medicine of Berlin, Germany

When is a hormone replacement therapy necessary?

- Menopausal symptoms
- Ovarian insufficiency caused by surgical removal of ovaries or due to chemotherapy or radiotherapy
- Primary ovarian insufficiency

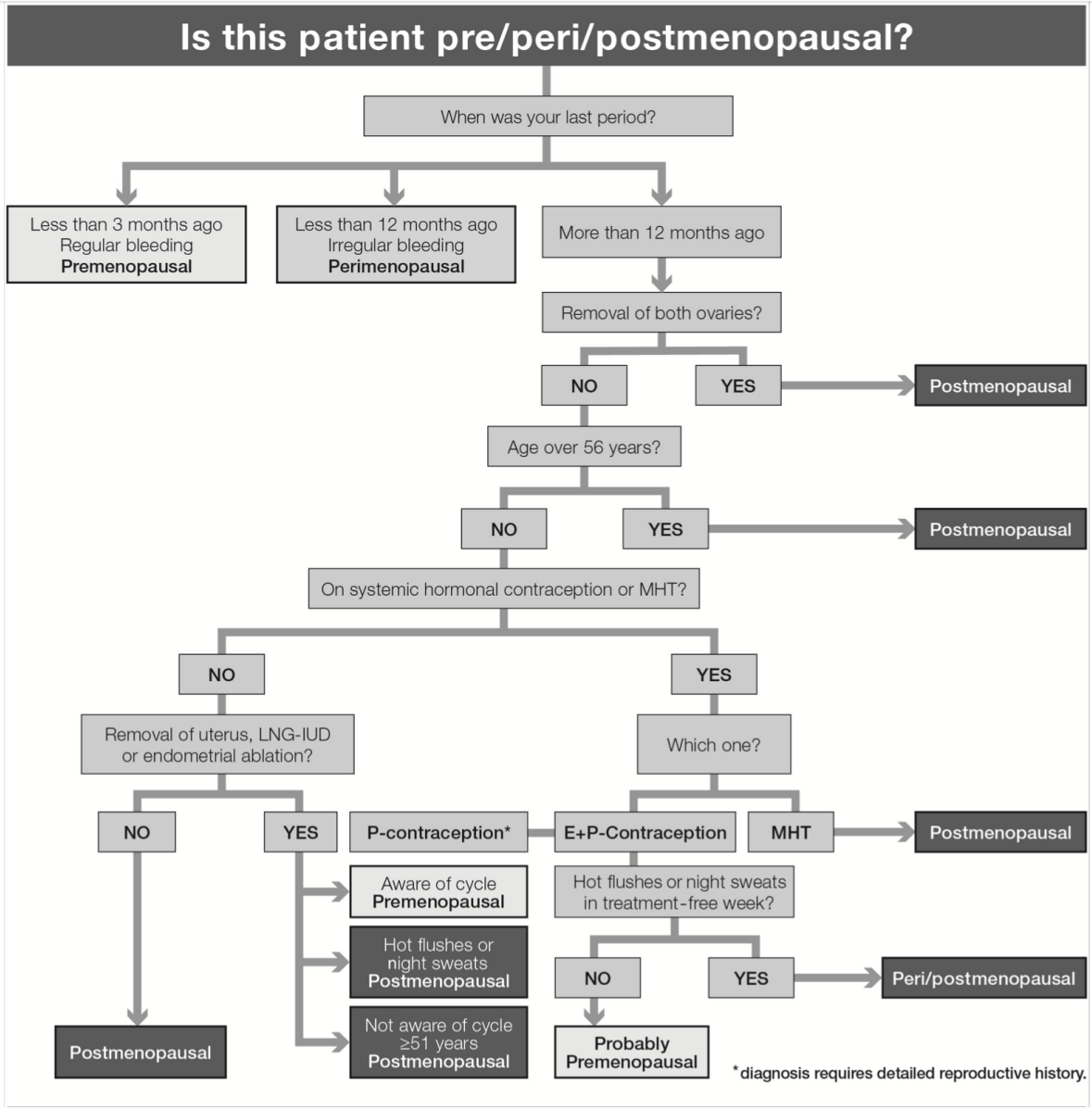
Menopause



Definition:

- Absence of period for 1 year
- Menopausal Transition: Period from normal ovarian function to ovarian failure
- Estrogen Deficiency
- Early Menopause: between 40 and 45 years
- Premature Ovarian Insufficiency < age of 40

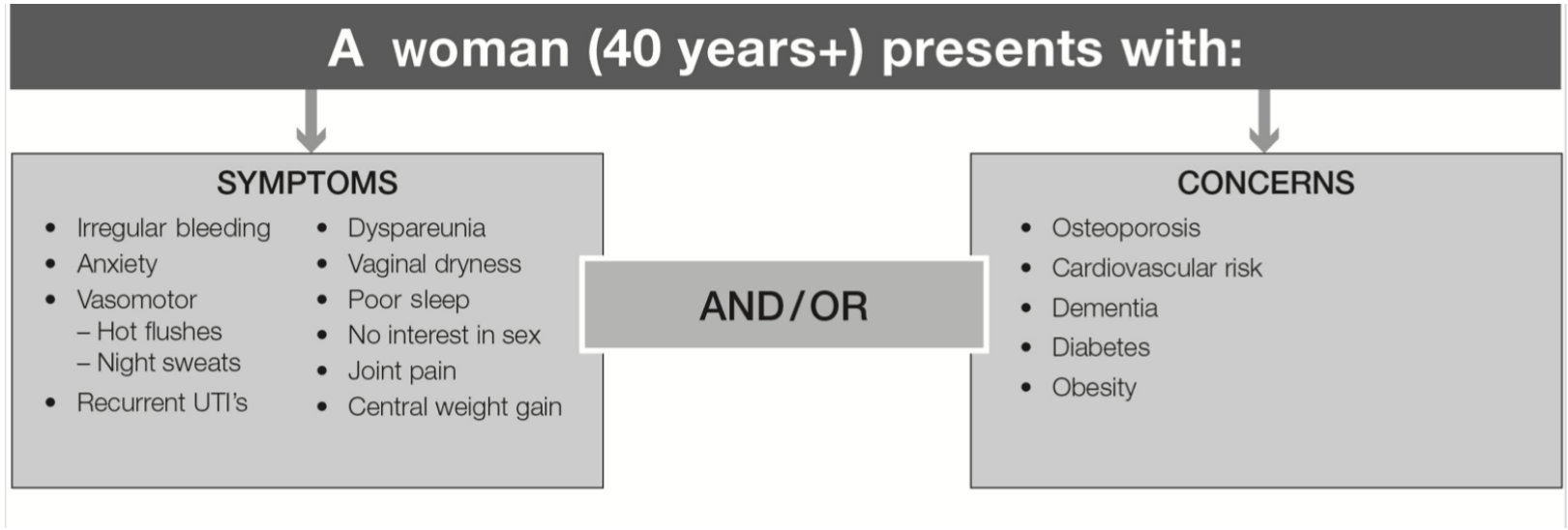
Santoro N. J Women`s Health 2018



F. M. Jane & S. R. Davis (2014) A Practitioner's Toolkit for Managing the Menopause, Climacteric, 17:5, 564-579

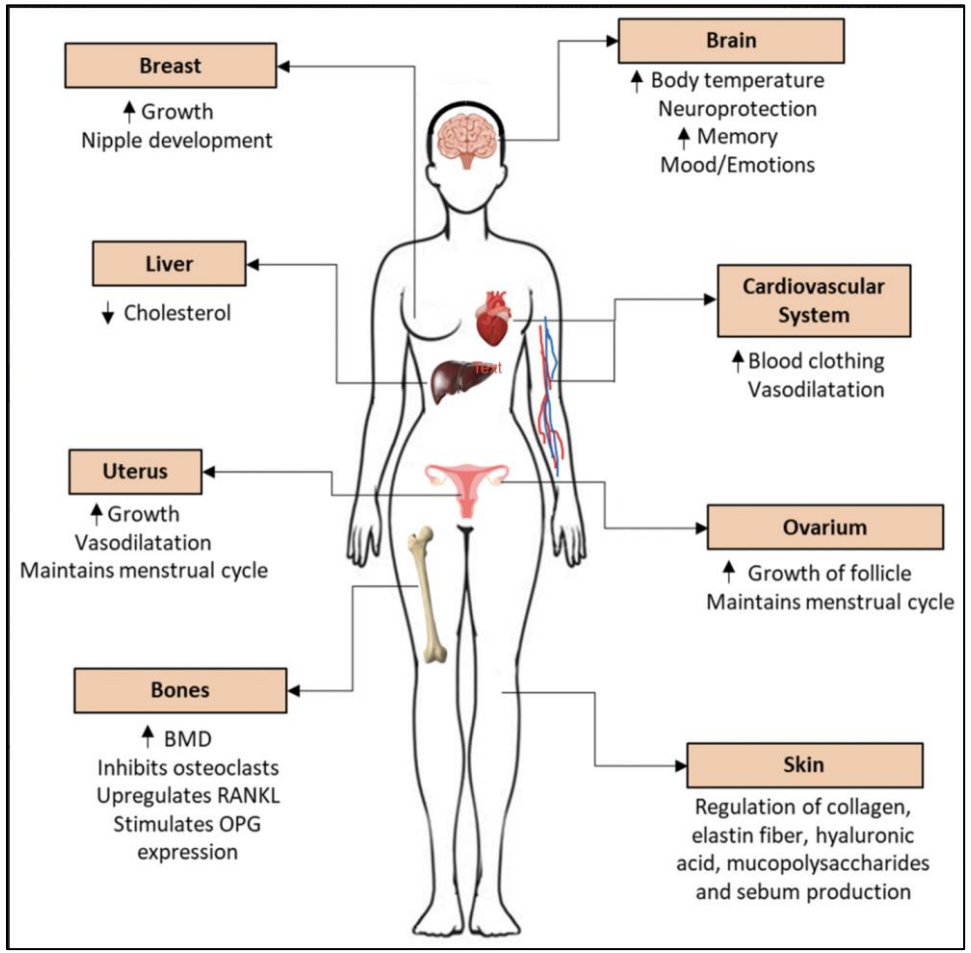
- Hormone diagnostic is rarely necessary
- Hormone diagnostic if age < 45
- FSH > 25 IU/L in two measurements > 4 weeks

Menopausal symptoms or concerns



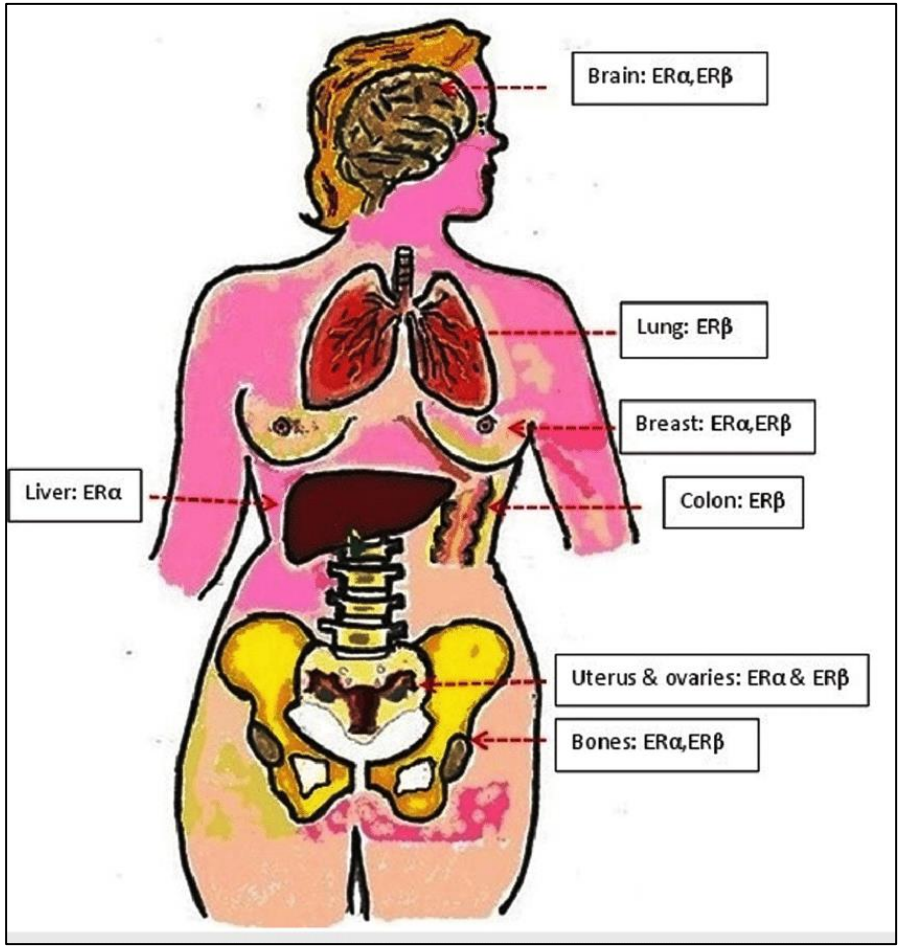
F. M. Jane & S. R. Davis (2014) A Practitioner's Toolkit for Managing the Menopause, Climacteric, 17:5, 564-579

Estrogen effects on the body



Role of E2 in a tissue-specific manner

Farkas, S. et al. *Biomedicines* **2022**, *10*, 861. https://doi.org/10.3390/ biomedicines10040861



The distribution of ER subtypes in the human body

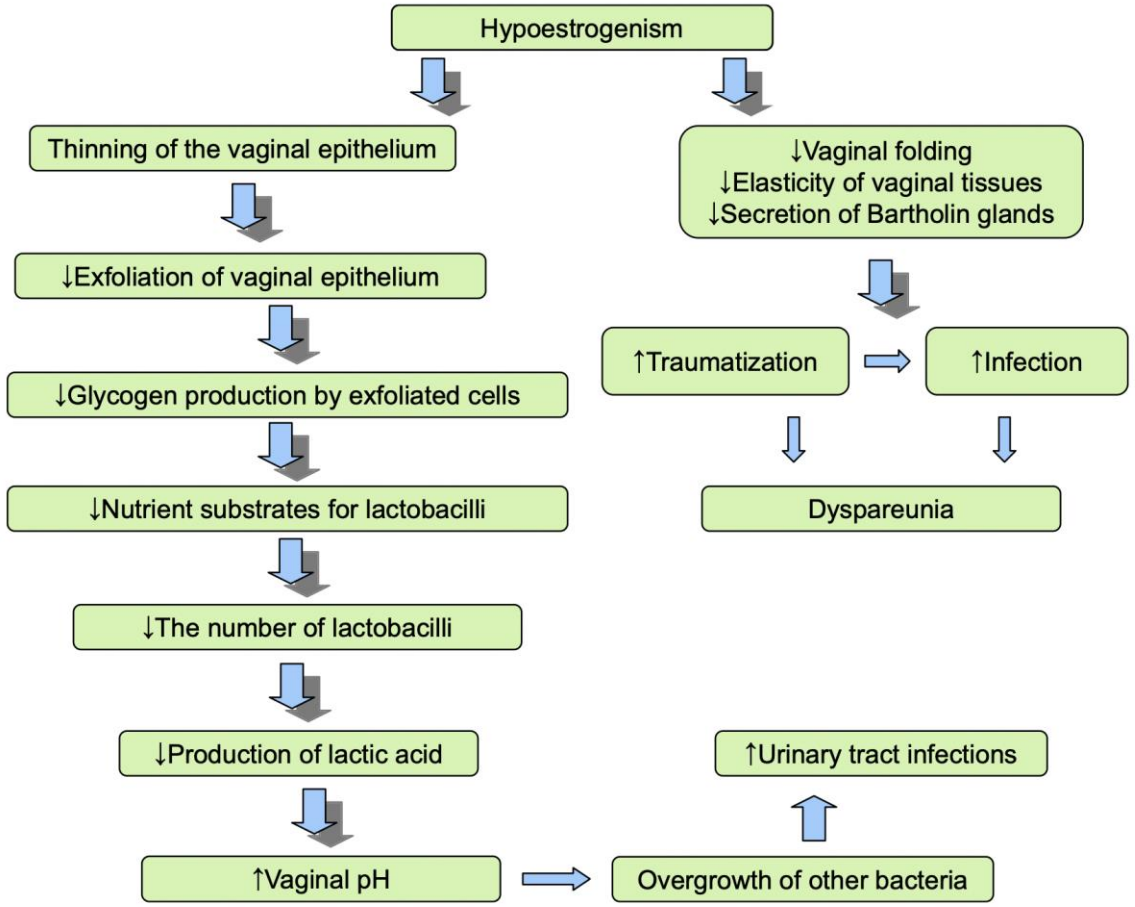
Barron et al. Cureus **2021** 13(11): e19994. DOI 10.7759/cureus.19994

Hot Flashes

- Hot flashes (HFs) are transient sensations of heat, sweating, flushing, anxiety, and chills lasting for 1–5 min
- abnormal hypothalamic thermoregulatory control resulting in abnormal vasodilatory response to minor elevations of core body temperature.
- Approximately affecting 85 % of all postmenopausal women
- The mean duration of HFs is 5 years with 1/3 of the women experiencing even 10 years
- Obesity is a risk factor

Menopausal Hot Flashes: A Concise Review J Midlife Health. 2019 Jan-Mar; 10(1): 6–13.

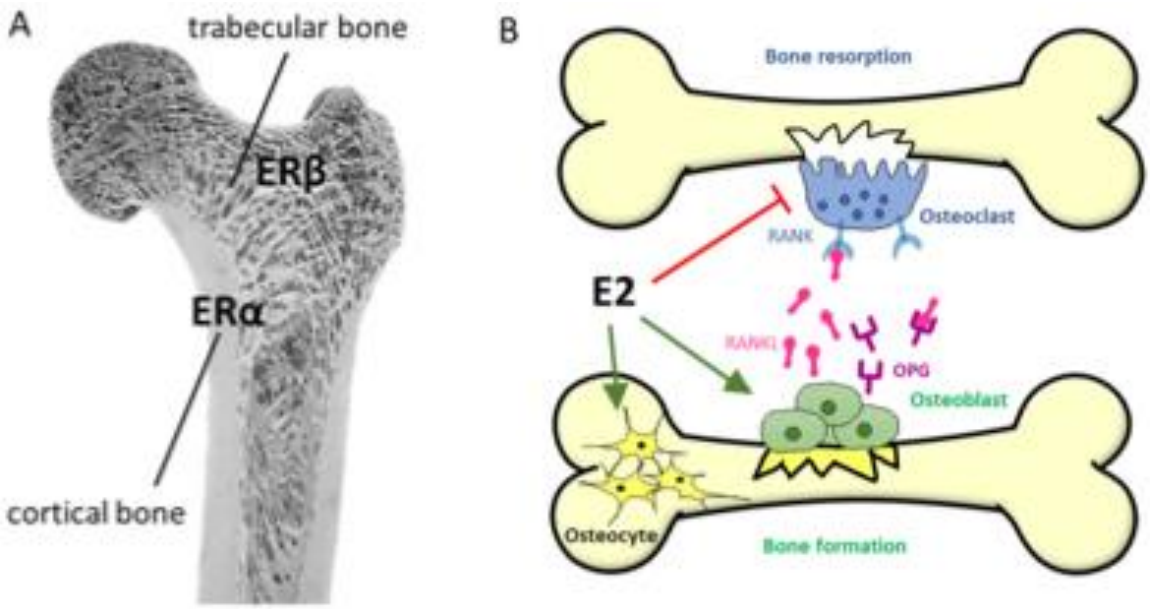
Vulvovaginal atrophy (VVA)



- Vulvovaginal atrophy (VVA) is a silent epidemic that affects up to 50%–60% of postmenopausal women
- Dryness, burning, itching, vaginal discomfort, pain and burning when urinating, dyspareunia, and spotting during intercourse

Naumova et l. International Journal of Women's Health 2018:10 387–395

Bone Loss and Osteoprosis



- Bone metabolic disease associated weakened bone microstructure and with bone loss and risk of fractures
- Estrogen's influence on bone formation is associated with stimulation of osteoblasts and inhibition of osteoclasts

E2—17β-estradiol; Erα—estrogen receptor alfa; Erβ—estrogen receptor beta;
OPG—osteoprotegerin; RANK—receptor activator NF-κB; RANKL—RANK ligand

Farkas, S. et al. *Biomedicines* 2022, *10*, 861. https://doi.org/10.3390/ biomedicines10040861

Aprroved indications for HRT

The goal of menopausal hormone therapy (MHT) with either estrogen (ET) alone or of a combination from estrogen and progestogens (EPT) is to alleviate the menopausal symptoms and improve quality of life

- Vasomotor symptoms
- Prevention of bone loss
- Premature ovarian insufficiency
- Genitourinary symptoms

The MHT does not provide contraception

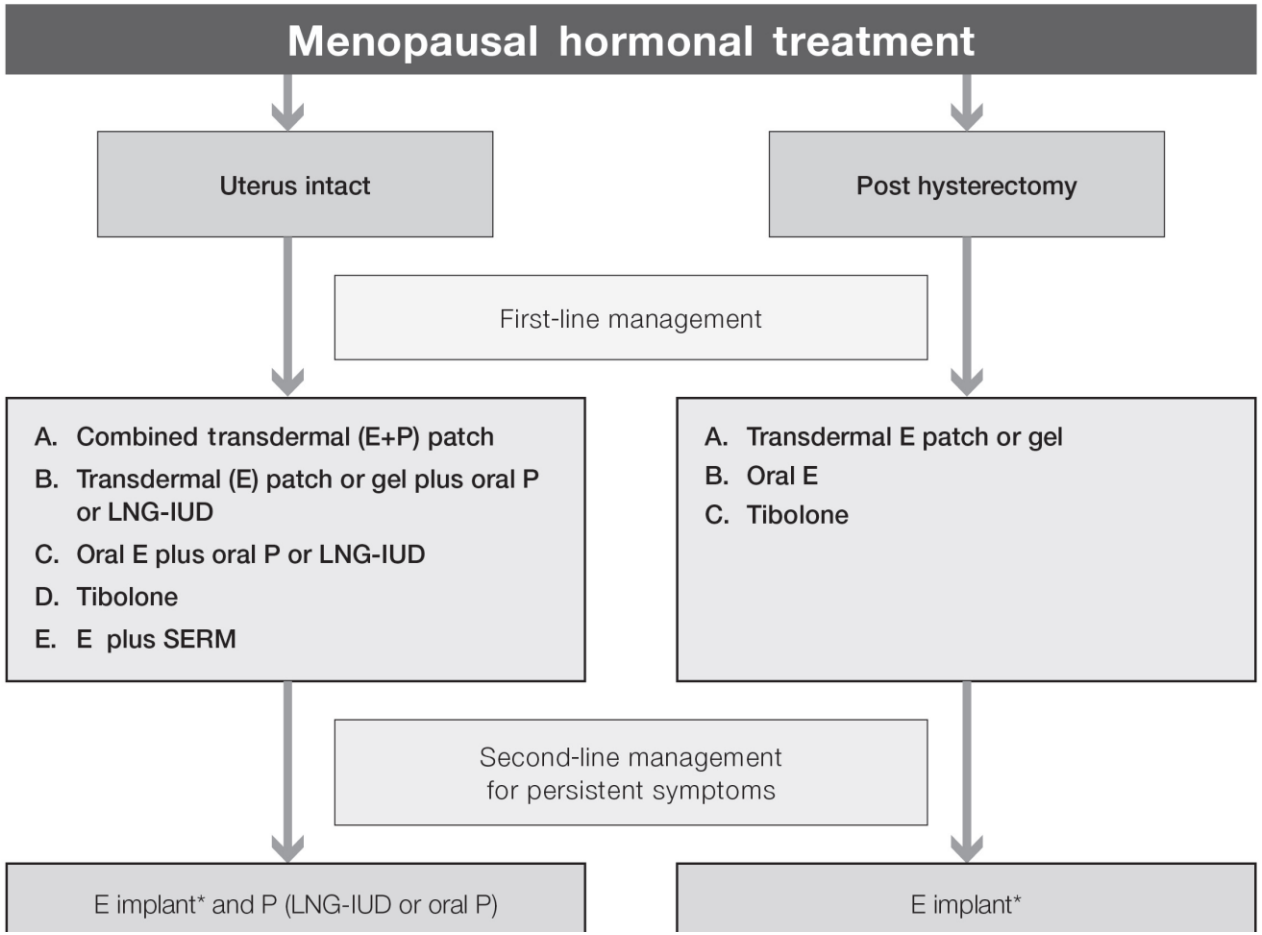
Contraindications for HRT

- Current, past or suspected breast cancer
- Estrogen-sensitive malignant tumor
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- Previous idiopathic or current venous thromboembolism
- Active or recent arterial thromboembolic disease (angina, myocardial infarction)
- Untreated hypertension
- Active liver disease
- Porphyria cutanea tarda

Forms of application

https://www.shecares.com/hormones/medical-treatments/hrt/ert-forms

Hormone Therapy



Women with intact uterus should receive a combined estrogen and progesterone therapy
with sufficient progestogen for at least 12-14 days per months for endometrial protection

F. M. Jane & S. R. Davis (2014) A Practitioner's Toolkit for Managing the Menopause, Climacteric, 17:5, 564-579

MHT dosing[1]

Estrogen

	Low dose	Moderate dose	High dose
CEE	0.3 – 0.45 mg/day	0.625 mg/day	1.25 mg/day
17β-estradiol	0.5 –1.0 mg/day	1.5 – 2 mg/day	2 mg
Estradiol valerate	0.5 mg/day	1 mg/day	2 mg/day
Transdermal estradiol patch	25 – 37.5 µg/day	50 µg/day	75 – 100 µg/day
Estradiol hemihydrate gel	0.5 mg/day	1.0 mg/day	1.5 mg/day

Sequential P – daily dose for 14 days per month- lowest "safe" dose with:

	Low dose E	Moderate to high dose E
Dydrogesterone	5 mg	10 mg
Micronized progesterone	100 mg	200 mg
MPA	5 mg	5 – 10 mg
Norethisterone acetate (NETA)	1.25 mg	1.25 – 2.5 mg

Continuous P – daily dose – lowest "safe" dose with:

	Low dose E	Moderate to high dose E
Dydrogesterone	5 mg	5 – 10 mg
Drospirenone	0.5 mg	—
Micronized progesterone	100 mg	100 mg
MPA	2.5 mg	2.5 – 5 mg
Norethisterone acetate (NETA)	0.5 – 1.0 mg	>1.0 – 2.5 mg
LNG-IUD	device releasing 20 µg/24 hours	

Tibolone

Tibolone	2.5 mg daily

F. M. Jane & S. R. Davis (2014) A Practitioner's Toolkit for Managing the Menopause, Climacteric, 17:5, 564-579

Is the HRT safe?

Women`s Health Initiative Clinical Trials

- WHI studies designed to prevent heart disease, breast and colorectal cancer and osteoprosis
- Enrolled 161 808 women between 1993-1998 in 40 centres, was sheduled to end in 2005
- The EPT cohort involved 16 608 women who received either combination HRT or placebo
- The ET cohort involved 10 739 postmenopausal women, aged 50-79 years, with prior hysterectomy to either E or placebo
- In 2002 the study was stoped due to high risk:

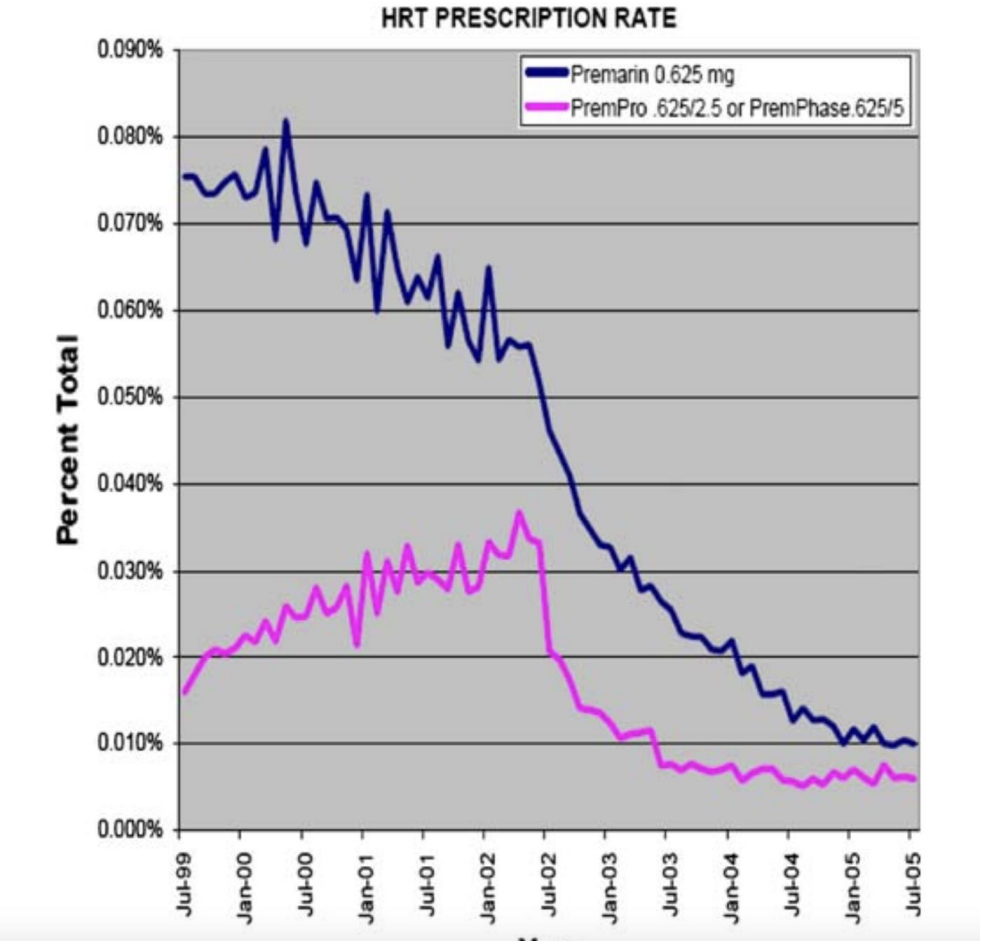
- 26 % increase in breast cancer
- 41 %increase in strokes
- 29 % increase in heart attacks
- Doubled rates of blood cloths

WHI Results

	CEE + MPA	CEE
	/10 000	/10 000
Coronary heart disease	+ 7	-5
Storke	+8	+12
Venous thromboembolic disease	+18	+7
Breast Cancer	+8	-7
Colorectal cancer	-7	+1
Endometrial cancer	-7	
Osteoprotic fractures	-5	-6
Diabetes	-16	-21
Mortality	-1	+3
Global index	+ 19	+2

Rossouw et al JAMA. 2002;288(3):321-333. doi:10.1001/jama.288.3.321
Anderson at al 2004 Apr 14;291(14):1701-12. doi: 10.1001/jama.291.14.1701

Misinterpretation of the results affected HRT prescription rate

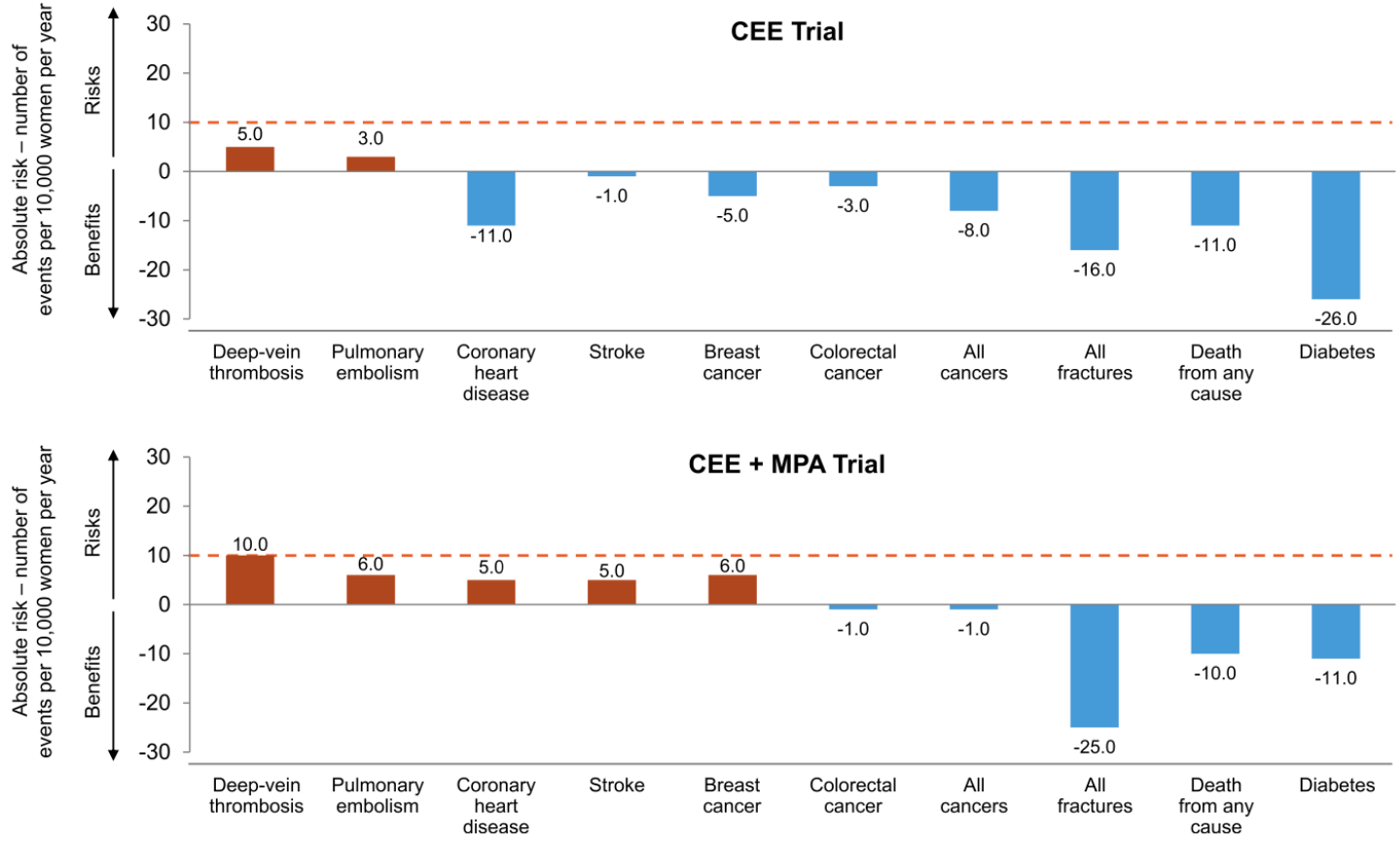


Parente et al .Arch Gynecol Obstet (2008) 277:219–224

	ET	EPT
Median age (years)	67	66
BMI > 30 kg /m^2	45 %	34 %
Smokers	48 %	50 %
Arterial Hypertension	48 %	36 %

10 % of the study population had additional risk factors such as history of venous thromembolic diesease, stroke, heart attack, diabetes, coronay heart dieseae

Benefits and risks for women aged 50-59



- Women receiving hormone replacement therapy early after menopause had a significantly reduced risk of mortality, heart failure, or myocardial infarction
- ” Window of opportunity”- HT initiation before 60 years of age and/or within 10 years of menopause and continued for 6 years or more
- In the 50-59 age group (HR, 0.61; risk reduction for CHD)

Menopause: The Journal of The North American Menopause Society
Vol. 29, No. 7, pp. 767-794, DOI: 10.1097/GME.0000000000002028

BMJ 2012;345:e6409 doi: 10.1136/bmj.e6409
Climacteric. 2012 June ; 15(3): 217–228.
doi:10.3109/13697137.2012.656401

HRT

- The increased absolute risk associated with EPT and ET are rare <10/10 000 and include increased risk of VTE
- EPT is associaed with increased risk of stroke and breast cancer
- If estrogen is inadequately opposed there is an increased risk of hyperplasia and endometrial cancer
- Increase of breast cancer risk is considered after 5 years duration of theray
- The type of progesteron may contibute to the breast cancer risk
- ” When the use of progesterone is necessary, micronizied progesterone is considered the safer alternative”

Breast Cancer Risk in Postmenopausal Women Using Estradiol–Progestogen Therapy

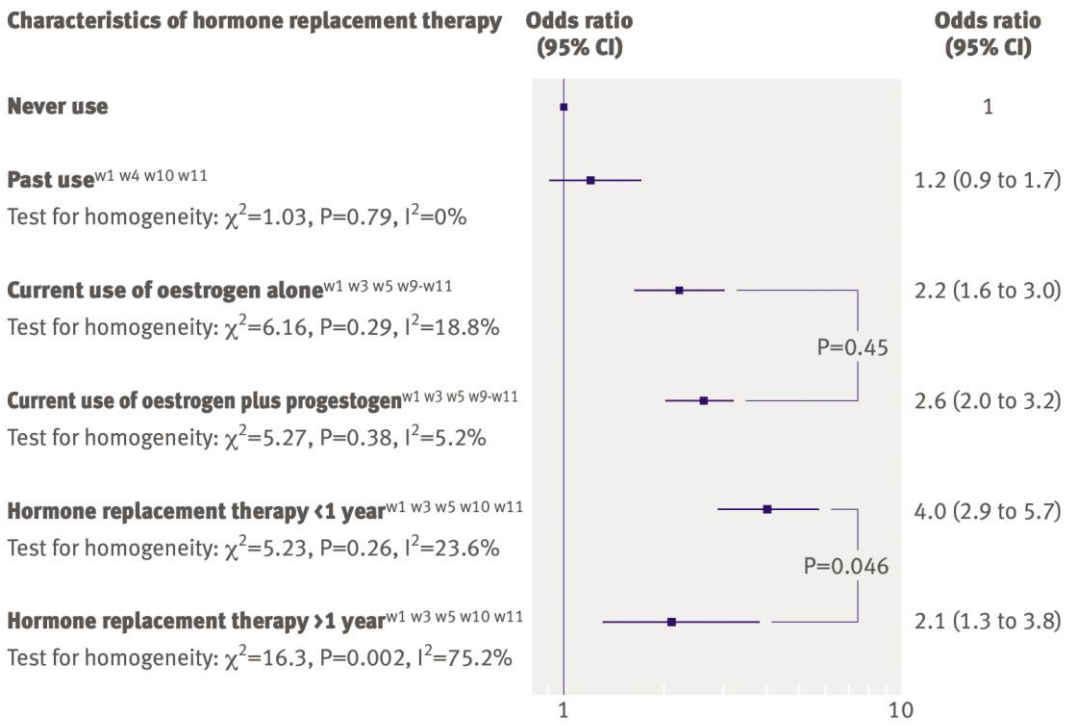
Table 4. Standardized Incidence Ratios of Invasive Breast Cancer Among Women Using Estrogen–Progestogen Therapy in 1994-2005, Grouped According to the Progestogen and Duration of Use*

Progestin Type and Duration	N	Observed	Expected	SIR	95% CI
6 mo to less than 3 y†					
Norethisterone acetate	22,368	439	424	1.04	0.94–1.14
Medroxyprogesterone	13,438	336	324	1.04	0.93–1.15
Dydrogesterone	7,420	87	85	1.02	0.82–1.26
Other‡	7,213	149	134	1.11	0.94–1.30
3 y to less than 5 y†					
Norethisterone acetate	12,211	266	169	1.34	1.17–1.51
Medroxyprogesterone	8,648	166	130	1.27	1.09–1.48
Dydrogesterone	3,413	32	26	1.22	0.83–1.72
Other‡	4,357	61	55	1.12	0.85–1.43
5 y or more§					
Norethisterone acetate	24,093	670	330	2.03	1.88–2.18
Medroxyprogesterone	19,299	454	277	1.64	1.49–1.79
Dydrogesterone	1,014	8	7	1.13	0.49–2.22
Other‡	5,804	159	77	2.07	1.76–2.04
Mixed‖	39,727	860	498	1.73	1.61–1.84
10 y or more§					
Norethisterone acetate	4,081	67	21	3.15	2.44–4.00
Medroxyprogesterone	2,049	16	8	1.90	1.07–3.07
Dydrogesterone	61	–	0.33	0.00	0.00–11.01
Other‡	289	6	2	2.79	1.02–6.07
Mixed‖	6,492	70	30	2.33	1.82–2.94

Heli Lyytinen et al. Obstet Gynecol 2009;113:65–73

- 221,551 Finnish women over 50 years using E2– progestogen therapy for at least 6 months in 1994–2005 were identified from the national medical reimbursement register and followed up for breast cancer incidence (n=6,211 cases) to the end of 2005
- Use of E2–progestogen therapy is associated with an increased risk for breast cancer after 3 years of use. The risk is lower for sequential than for continuous use

Risk of VTE by characteristics of HRT



- Meta-analysis of observational studies showed that oral oestrogen but not transdermal oestrogen increased the risk of venous thromboembolism.
- The risk of venous thromboembolism in women using oral estrogen was higher in the first year of treatment compared with treatment for more than one year.

Canonico Met al BMJ. 2008 May 31;336(7655):1227-31. doi: 10.1136/bmj.39555.441944.BE

Risk of Stroke With Various Types of Menopausal Hormone Therapies. A National Cohort Study

- 980 003 women aged 51 to 70 years from 1995 to 2010 from 5 Danish registries
- 20 199 suffered a stroke
- In total, 36% of women used hormone therapy.
- Current use conferred a relative rate of 1.16 (95% confidence interval, 1.12-1.22).
- Compared with never users, the increased rate ratio of all stroke with continuous, cyclic combined estrogen/progestin, and estrogen only oral therapies were 1.29, 1.1, and 1.18.
- The increased risk was because of ischemic stroke, but not hemorrhagic stroke.
- **Transdermal application of hormone therapy was not associated with risk of stroke**

Stroke. 2017;48:2266-2269. DOI: 10.1161/STROKEAHA.117.017132.

HRT after breast cancer

Characteristic	No. of events (No. of women in subset)	HR (95% CI)	*P* value‡ (χ^2)
All women	56 (442)	2.4 (1.3 to 4.2)	.003
All women, adjusted	52 (416)	2.2 (1.0 to 5.1)	.013
Hormone receptor positive	37 (268)	2.6 (1.3 to 5.4)	.009
Hormone receptor negative	19 (174)	1.8 (0.7 to 4.8)	.205
Tamoxifen	18 (153)	4.7 (1.4 to 16.2)	.015
No tamoxifen	38 (289)	1.9 (1.0 to 3.6)	.067
HT before diagnosis	26 (230)	2.3 (1.0 to 5.3)	.049
No HT before diagnosis	26 (186)	2.2 (1.0 to 5.1)	.061
Node negative	30 (282)	2.4 (1.1 to 5.4)	.026
Node positive	18 (110)	2.3 (0.8 to 6.4)	.117

Holmberg et al J Natl Cancer Inst 2008;100:475–482

- 442 women with history of breast cancer: 221 received HT, 221 controls
- Cumulative incidences at 5 years were 22.2% in the HT arm and 8.0% in the control arm
- There was a clinically and statistically significant increased risk of a new breast cancer event in survivors who took HT

HRT Alternatives

Evidence-based non-hormonal treatment [1] for vasomotor symptoms

Estrogen and SERM therapy

CEE 0.45 mg plus bazedoxifene	20 mg daily
SSRI or SSRI/SNRI– low dose (also treats menopausal mood disorder)	Venlafaxine 75mg, desvenlafaxine 50mg, escitalopram 10 mg, paroxetine 7.5 mg daily
Clonidine	100 µg daily
Gabapentin	300 – 900 mg daily
Pregabalin	75 – 150 mg twice a day
Hypnosis	
Cognitive behavior therapy	
Weight loss for obese women	
Stellate ganglion blockade*	Severe resistant VMS *specialist referral

[1] – Availability of hormonal/nonhormonal treatment and indications for use from regulatory bodies vary between countries.

F. M. Jane & S. R. Davis (2014) A Practitioner's Toolkit for Managing the Menopause, Climacteric, 17:5, 564-579

HRT and risk of endometrial cancer

Table 2. BMI-endometrial cancer risk associations stratified by population type and HRT use using the piecewise model

	No. of studies	Risk ratio (95% CIs)				
		22 kg/m^2	27 kg/m^2	32 kg/m^2	37 kg/m^2	42 kg/m^2
Total	24	1.00	1.22 (1.19, 1.24)	2.09 (1.94, 2.26)	4.36 (3.75, 5.10)	9.11 (7.26, 11.51)
Population type						
North American	8	1.00	1.21 (1.14, 1.29)	2.08 (1.66, 2.60)	4.33 (2.77, 6.78)	9.01 (4.61, 17.65)
European	13	1.00	1.21 (1.18, 1.23)	2.04 (1.89, 2.21)	4.18 (3.56, 4.90)	8.54 (6.72, 10.85)
Asia-Pacific	2	1.00	1.27 (1.16, 1.40)	2.49 (1.74, 3.58)	6.23 (3.02, 12.83)	15.53 (5.25, 45.97)
Multiethnic	1	1.00	1.28 (1.20, 1.36)	2.52 (1.99, 2.54)	6.35 (3.87, 10.45)	15.99 (7.61, 33.79)
HRT use						
Never	3	1.00	1.31 (1.20, 1.42)	2.74 (2.02, 3.73)	7.54 (4.09, 13.90)	20.70 (8.28, 51.84)
Combined HRT	3	1.00	1.08 (1.02, 1.14)	1.34 (1.08, 1.65)	1.78 (1.17, 2.72)	2.38 (1.26, 4.50)
Any HRT	5	1.00	1.07 (1.03, 1.12)	1.30 (1.10, 1.53)	1.68 (1.21, 2.33)	2.18 (1.33, 3.55)

CI; confidence interval., HRT: hormonal replacement therapy.

Continous EPT in obesity women reduced the risk of endometrial cancer

Crosbie et al. Cancer Epidemiol Biomarkers Prev; 19(12); 3119–30

Association between various hormone therapy regimens and endometrial cancer risk, by duration of use for the 1997-1999 study and the combined studies from 1985-1999

	1997–1999 only*				Overall (1985–1999)†			
Type/duration of therapy	Cases (n)	Control subjects (n)	OR‡	95% CI	Cases (n)	Control subjects (n)	OR‡	95% CI
No hormone therapy	145	181	1.0	Reference	531	965	1.0	Reference
Estrogen alone	34	9	6.7	2.7–16	341	179	4.6	3.6–5.9
6 mo–<3 y	15	5	3.3	1.1–10	77	86	1.9	1.4–2.7
3–<6 y	7	1	13	3.7–48	42	34	2.6	1.6–4.2
≥6 y	12	3	13	3.7–48	222	59	11	7.7–15
Sequential, progestin <10 d/mo	13	4	11	2.9–40	47	37	3.8	2.3–6.2
6 mo–<3 y	2	1	2.3	0.16–32	14	15	2.4	1.1–5.4
3–<6 y	3	0	15	3.5–66	8	9	3.2	1.1–8.7
≥6 y	8	3	15	3.5–66	25	13	5.9	2.9–12
Sequential, progestin 10–24 d/mo	22	39	1.3	0.68–2.6	62	129	1.3	0.93–1.9
6 mo–<3 y	5	12	1.1	0.32–3.6	17	49	0.94	0.51–1.7
3–<6 y	4	9	1.1	0.29–4.3	15	39	1.2	0.60–2.2
≥6 y	13	18	1.6	0.66–3.9	30	41	2.0	1.2–3.5
Continuous combined	43	105	0.57	0.35–0.93	52	138	0.59	0.40–0.88
6 mo–<3 y	10	33	0.42	0.19–0.97	14	49	0.45	0.23–0.88
3–<6 y	9	24	0.48	0.20–1.2	11	33	0.51	0.24–1.1
≥6 y	24	48	0.74	0.40–1.4	27	56	0.77	0.45–1.3

Doherty JA, Cushing-Haugen KL, Saltzman BS, et al. Long-term use of postmenopausal estrogen and progestin hormone therapies and the risk of endometrial cancer. Am J Obstet Gynecol 2007;197:139.e1-139.e7

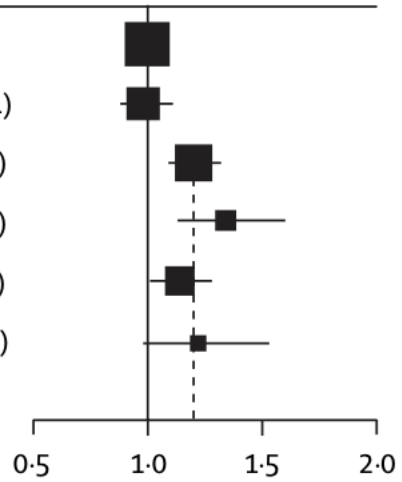
HRT after endometrial cancer

- One randomised trial and five observational studies included 896 EC survivors who used HRT and 1079 non-users.
- 19 of the 896 HRT users experienced recurrence, whereas 64 of the 1079 controls did.
- The meta-analysis indicates no significant increase in the risk of recurrence in EC survivors using HRT relative to the control group (OR: 0.53; 95% confidence interval: 0.30–0.96)
- Other alternatives should be explored first since studies are not uniform
- HRT in uterine sarcomas should be avoided

S.-H. Shim et al. / European Journal of Cancer 50 (2014) 1628–1637

HRT and risk of ovarian cancer

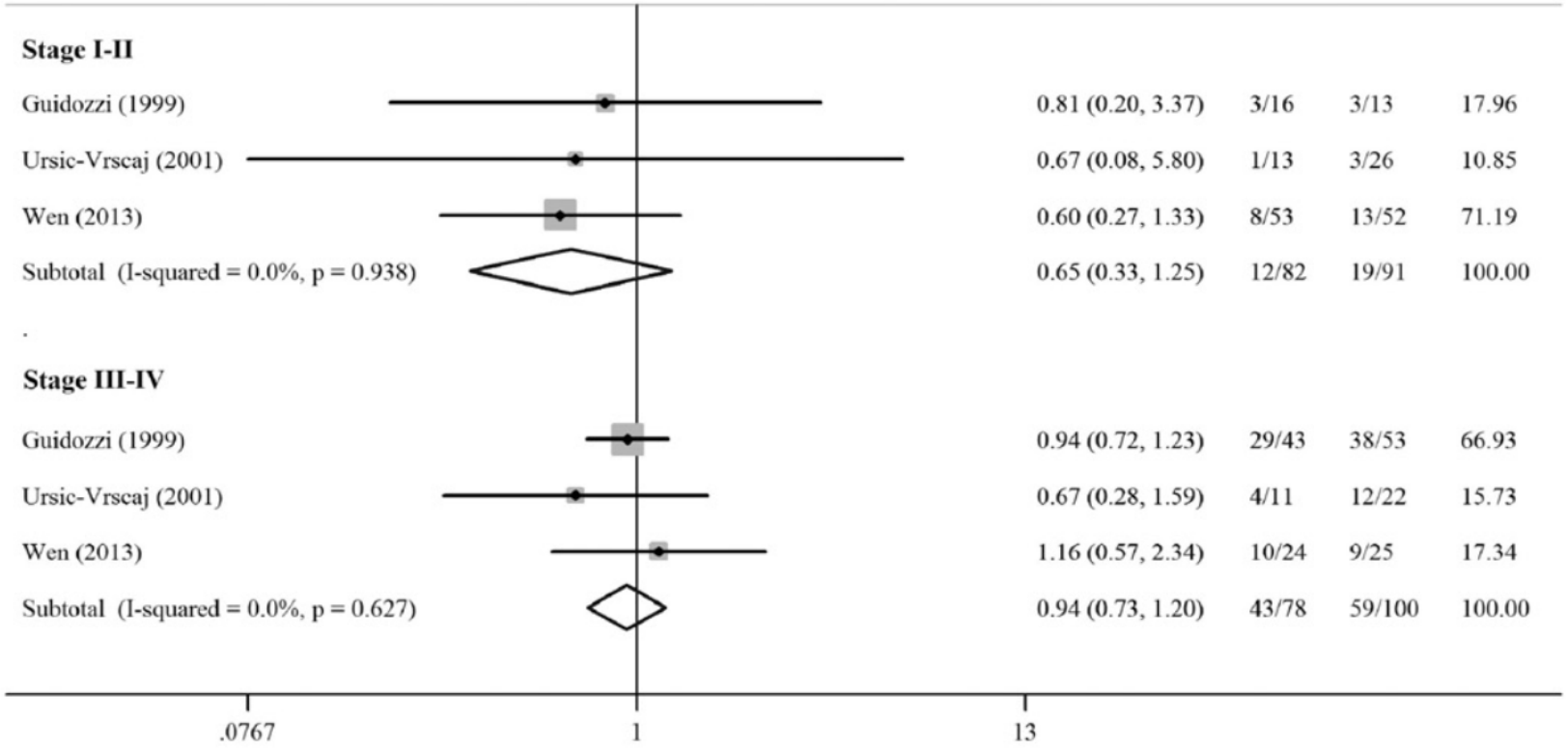
Last reported HRT use	Years of HRT use*	Cases/ population (1000s)	Relative risk (95% CI)
Never users	..	1142/474·7	1·00
Past users	3·3	391/186·8	0·98 (0·88–1·11)
All current users	7·7	740/287·1	1·20 (1·09–1·32)
Oestrogen-only	9·2	242/85·9	1·34 (1·13–1·60)
Oestrogen+progestagen	6·9	414/169·3	1·14 (1·01–1·28)
Other	7·0	84/31·9	1·22 (0·98–1·53)



- 48 576 postmenopausal women from the UK Million Women Study
- After follow-up of 5.3 years current users were significantly more likely to develop ovarian cancer than never users (relative risk 1·20 [95% CI 1·09–1·32; p=0·0002] for incident disease

Ovarian cancer and hormone replacement therapy in the Million Women Study
Lancet 2007; 369: 1703–10

HRT after ovarian cancer



- Postoperative HRT does not have a negative effect on overall survival and tumour recurrence
- However the HRT should be avoided in granulosa cell tumours

Li et al. / Gynecologic Oncology 139 (2015) 355–362

HRT in women with early natural or surgical menopause

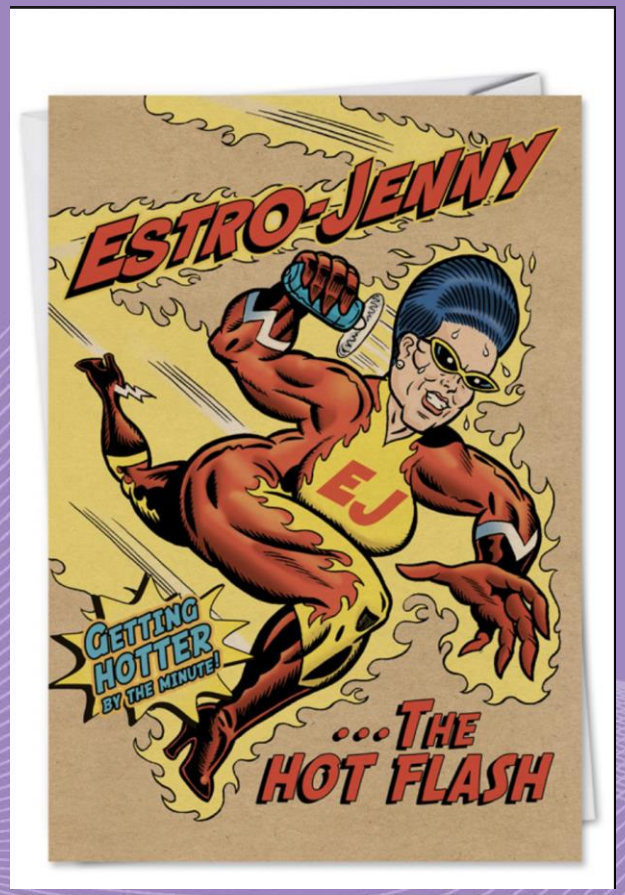
- Early HRT is indicated to reduce the risk of osteoprosis and related fractures and to reduce vasomotor symptoms
- Data from observational studies suggest benefit for prevention of CHD and atherosclerosis and reduction of cognitive decline
- Estrogen-Level should achieve 100 pg/nl
- Patch 100mcg/d; Gel 1,5 mg; oral 2 mg Estrogen per day
- Progesterone: CMA 2 mg or micronizied Progesterone 200 mg for at least 12 days per month

Phytoestrogens

- A class of compounds, non-steroidal, either of plant origin or metabolically derived from plant precursors
- 3 classes: isoflavones, lignans or coumestans
- Isoflavones are found in beans or legumes with soybeans and soy products the most popular (30-60 mg per day)
- Lignans are found in unrefined grains, cereal, flaxseed
- Coumestans are found in alfalfa and clover sprouts
- They resemble estrogen and have weak estrogenic activity and also antagonist properties
- Hypercium perforatum (300 mg per day)
- Yam is the common name for some plant species in the genus Dioscorea that form edible tubers (no effect in placebo–controlled studies)

Summary

- HRT is an effective therapy for reduction of vasomotor symptoms and bone loss prevention
- Individual risk factors should be evaluated before initiation
- ”Windows of opportunity” for therapy begin
- Alternatives if there is contraindication for HRT
- Periodic assessment of the need for ongoing use of hormone therapy should be individualized on the basis of a woman’s menopause symptoms, general health and underlying medical conditions, risks, treatment goals, and personal preferences



Thank you!

engage@esgo.org
engage.esgo.org

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