

Debate

**Progestin or progesterone:
there is no real difference
- for the motion -**

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Conflicts of interest

Member of an advisory board for Women's health issues of the Federal Centre for Health Information in Germany:

<http://www.frauengesundheitsportal.de>

Participation in a phase III study of a drug tested for prevention of osteoporosis in postmenopausal women in the past (Pfizer, USA)

Hot flushes

„The progestogens ...were norethisterone, norethisterone acetate, levonorgestrel, nomogestrol acetate, medroxyprogesterone acetate, cyproterone acetate and micronized progesterone.

...evaluation of the effect of different types, doses and modes of progestogen therapy on vasomotor symptoms would be best estimated in a separate review with trials selected specifically to address these questions.“

MacLennan AH et al. Oral oestrogen and combined oestrogen / progestogen therapy versus placebo for hot flushes. *Cochrane Database Syst Rev* 2004 (3)

„The **influence of** progestin or progesterone use, cyclic and continuous regimens,

and differences in adverse effects could not be determined.“

Heidi Nelson

Commonly used types of postmenopausal estrogen for treatment of hot flashes. Scientific Review. JAMA 2004; 291: 1610 - 1620

„A good-quality trial reported no differences between **progesterone** (32 mg/day) and placebo groups for vasomotor or somatic symptoms, mood, or sexual feelings.

A fair-quality trial (20 mg/day) reported significant reductions in vasomotor symptoms, but not depression scores, compared to placebo.“

(Progesterone=transdermal progesterone)

„None of the trials reported adverse effects.“

Summary:

„Trials of progestin indicate mixed results for treatment of vasomotor symptoms“

Nelson HD et al. Management of Menopause-Related Symptoms. Evidence Report/Technology Assessment No. 120. Agency for Healthcare Research and Quality. March 2005

Osteoporosis – hip fracture

Incidence reported in 4 trials (HERS 1998; WEST 2001; WHI 1998; WISDOM 2007).

combined continuous HT (HERS 1998; WHI 1998; WISDOM 2007)

oestrogen-only HT (WEST 2001; WHI 1998)

If data on combined HT, then: [MPA](#)

Clinical **vertebral fracture**:
Only WHI, only CEE+MPA

[Farquhar CM](#) et al. Long term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database Syst Rev 2005 (3).
New search for studies completed, Conclusions not changed (2008)

Urinary incontinence I

„The data considered in this review suggest that oestrogens can improve or cure urinary incontinence, but that combining progesterone with oestrogen increases incontinence.“

If estrogens were combined,
then bulk of data: CEE+MPA (due to HERS)

Moehrer B, Hextall A, Jackson S. Oestrogens for urinary incontinence in women. Cochrane Database Syst Rev 2003; (2); CD001405

Urinary incontinence II

Systematic review of randomized controlled trials:

Oral HT (17 RCTs; n=1243)

Transdermal / vaginal HT (5 RCTs, n=710)

Differences between the 2 sets of studies

Most data about **CEE+MPA** (WHI),
spurious data: dydrogesterone and NETA

Potential differential effects of progesterone/progestins
on incontinence: not analyzed

Shamliyan TA et al. Systematic review: randomized, controlled trials of nonsurgical treatments for urinary incontinence in women. *Ann Intern Med* 2008; 148: 459 – 473

Coronary events

myocardial infarction or cardiac death

Outcome measured in relatively healthy women in 5 trials (EPHT 2006; EPAT 2001; PEPI 1995; WHI 1998, WISDOM 2007)

If a progestin: then MPA

Outcome measured in women with cardiovascular disease in 6 trials (ERA 2000; ESPRIT 2002; EVTET 2000; HERS 1998; WAVE 2002; WEST 2001)

If a progestin: then MPA

Farquhar CM et al. 2008

Stroke

Outcome reported in relatively healthy women in 4 trials (EPHT 2006; EPAT 2001; PEPI 1995; WHI 1998)

If a progestin: then MPA

Outcome measured in women with cardiovascular disease in 5 trials (ESPRIT 2002; EVTET 2000; HERS 1998; WAVE 2002; WEST 2001)

If a progestin: then MPA

Farquhar CM et al 2008

Venous thromboembolism

Outcome measured in relatively healthy women in 4 trials (EPAT 2001; PEPI 1995; WHI 1998, WISDOM 2007)

Outcome measured in 5 trials of women with cardiovascular disease (ERA 2000; ESPRIT 2002, EVTET 2000; HERS 1998; WAVE 2002)

If a progestin: then MPA

Farquhar CM et al 2008

Breast cancer I

Meta-analysis of 13 studies of ET:
OR of 1.16 (95% confidence limits 1.06, 1.28)

Meta-analysis of 8 studies of CHT
OR of 1.39 (95% CL 1.12, 1.72)

No differentiation according to type of P

Shah NR et al. Postmenopausal hormone therapy and breast cancer: a systematic review and meta-analysis. *Menopause* 2005; 12: 668 - 678

Breast Cancer II

Annual increases
for EPT across study types are 0–9%, for ET 0–3%

Limitations discussed:

“Finally, given the lack of specific information on hormonal constituents, subanalyses addressing the issue of Potential differences between CEE-based and non-CEE based preparations were not possible, likewise **we could not differentiate between various progestins.**”

Greiser CM, Greiser EM, Dören M. Menopausal hormone therapy and risk of breast cancer: a meta-analysis of epidemiological studies and randomized controlled trials. Human Reprod Update 2005; 11: 561 - 573

Breast Cancer III

“We estimate that overall, EPT results in a 7.6% increase in breast cancer risk per year of use. The risk was statistically significantly lower in US studies than in European studies – 5.2 vs 7.9%.”

“There was a significantly higher risk for continuous-combined than for sequential EPT use in Scandinavian studies where much higher total doses of progestin were used in continuous-combined than in sequential EPT.”

Effect of NETA?

Lee SA et al. An overview of menopausal oestrogen-progestin hormone therapy and breast cancer risk. British Journal of Cancer 2005; 92: 2049 - 2058

Breast cancer IV

Across histological types, the relative risks associated with combined hormone therapy are generally higher than those associated with oestrogen-only therapy.

[Reeves GK](#) et al. Hormonal therapy for menopause and breast-cancer risk by histological type: a cohort study and meta-analysis. *Lancet Oncol* 2006; 7: 910 - 918

Breast cancer V

Outcome measured in relatively healthy women in 6 trials (EPHT 2006; EPAT 2001; Notelovitz 2002; PEPI 1995; WHI 1998; WISDOM 2007) with a total of 8 different interventions,

comprising comparisons of oestrogen-only HT, combined continuous HT and combined sequential HT versus placebo for varying durations from one year to over seven years

If a progestin: then MPA

Farquhar CM et al 2008

Endometrial cancer

Outcome measured in 7 trials (EPAT 2001; ESPRIT 2002; Ferenczy 2002; HERS 1998; Obel 1993; PEPI 1995; WHI 1998)

with a total of 11 different interventions, comprising comparisons of oestrogen-only HT, combined continuous HT and combined sequential HT versus placebo for varying durations from one year to over five years

Most data on MPA,
very few on [dydrogesterone and NETA \(2 studies\)](#),
combined with different estrogens

[Farquhar CM](#) et al 2008

Colorectal cancer

Outcome measured in 5 trials (EPAT 2001; HERS 1998; PEPI 1995; WHI 1998, WISDOM 2007) with a total of 5 different interventions,

comprising comparisons of oestrogen only HT, combined continuous HT and combined sequential HT versus placebo for varying durations from one year to almost seven years.

If a progestin, then: MPA

Farquhar CM et al 2008

Cognitive function(s) Probable dementia

Almost exclusively data from WHIMS and WHISCA

If a progestin: then MPA

Farquhar CM et al 2008

Problems with the evidence....

All of the statistically significant findings of this review derived from the two biggest trials, HERS 1998 and WHI 1998

However there is little evidence on the long term effects of HT on the healthy younger women who are most likely to use it for menopausal symptoms

and **nor is much known about** factors that may modulate the risks involved, ...**different oestrogens and progesterone's, different time frames for the use of HRT, and different doses and routes of administration.**

Farquhar CM et al 2008



WHI Legacy to Future Generations of Women Conference,
National Institutes of Health, February 28 - March 1, 2006

“Women are citizens with the right and responsibility to participate meaningfully in the decisions that affect their lives and to demand accountability from the people and institutions that have the duty to fulfill these rights.

Women are entitled to no less.

Let us work for no less.”

-The Wye River Call to Action for Global Women's Health (7 June 2005)

Not possible to decide – on the basis of results of randomized clinical trials with clinical outcomes –

IF there are differences among various progestational agents,

as the basis of evidence is dominated by studies utilizing MPA