

Consensus Statement

Consensus Statement

Optimising HRT

Every woman is different, it is therefore important to individualise therapy. As with other areas of medicine, we recommend using the lowest effective dose to relieve symptoms. A widening range of HRT regimens makes this possible.

- On the basis of patient history choose:
 - Type and route of HRT
 - Dose of HRT – usually starting with the lowest dose
- Adjust therapy according to individual response

What is the rationale for reducing dosage?

Menopausal symptoms may be controlled by lower HRT doses than previously used.^{1,2} These doses have also been shown to prevent osteoporosis.^{3,4}

- There are fewer side effects at lower doses, eg:
 - Estrogenic side effects
 - Nausea, bleeding, fluid retention, breast pain, headache
 - Progestogenic side effects
 - Migraine, bleeding problems, PMS-like side effects e.g. mood disturbance, bloating, acne, greasy skin
- Encourages continuation of therapy¹
- Endometrial protection is maintained with lower dose combined preparations^{5,6}
- May reduce the risk of venous thromboembolism⁷ (VTE) and stroke⁸

Prescribing HRT

- In general, start low and adjust as necessary
- Women with an early menopause (whether natural or induced) may need a higher dose to control symptoms than women who undergo menopause at a normal age
- Women with a uterus should always be prescribed a progestogen in addition to estrogen
- Women without a uterus should usually be prescribed estrogen alone
- Initial assessment of response / side effects should take place within three months with dose adjustment if appropriate
- Once therapy is established, assess benefits / risks at least annually

Duration of therapy

- In some women menopausal symptoms may continue indefinitely, therefore there should be no limit to duration of therapy
- Women with an early menopause should continue therapy at least until they reach the natural average age of the menopause (50/51 years of age)
- Continuation should be agreed on an individual basis
- The decision to continue / discontinue should be made jointly by an informed woman and her prescriber
- Clinical experience in general suggests that approximately 50% of women suffer resumption of symptoms following cessation of therapy
- If a woman wishes to discontinue, it is recommended that the dose is reduced in a stepwise manner – sudden cessation may provoke menopausal symptoms in the short term
- The appearance or re-appearance of distressing symptoms will require reassessment
- HRT can be restarted if symptoms persist, usually starting with the lowest dose

Putting the possible risks of breast cancer into perspective

- 1 About 3 women in every 1,000 aged 50-64 years living in the UK develop breast cancer each year. The incidence of breast cancer in this age group has changed little over the last ten years⁹
- 2 The risk of breast cancer does not appear to be increased amongst women who use estrogen-only HRT.^{10,11} Recent evidence shows that there is no increased risk of breast cancer in women with prior hysterectomy who use estrogen only therapy.¹² There is some evidence that women who use combined HRT (estrogen and progesterone) may have a slightly increased risk of breast cancer.^{13,14}
- 3 With combined therapy both continuous and sequential there may be up to 4 additional cases for every 1,000 women over a five year period—additional to the 15 that occur without using HRT.¹ There is some evidence that risk may increase with duration of use.¹⁵
- 4 Some studies have found that after stopping use of combined HRT for a period of five years, a woman's risk returns to baseline.¹³

The risk of breast cancer may be increased in women who are overweight,^{16,17} those who smoke heavily^{18,19} and those who are heavy drinkers of alcohol.^{20,21} Each of these three factors may increase the chances of developing breast cancer to a greater extent than combined hormone replacement therapy.

Regular breast screening (mammography) can detect breast cancer early. Early breast cancer usually requires less radical treatment and the outlook is much better than in cases diagnosed late. All women should attend their mammography screening clinic regularly and remain breast aware.

¹ Most studies show either no increase or a small increase in breast cancer with HRT.^{13,15}

Other risks

- 1 In common with most other oral exogenous estrogen, HRT is associated with an increase in risk of venous thromboembolism (VTE),²² however, some studies indicate that this risk is limited to the first year of use²³. Non-oral HRT is not associated with an increased risk of VTE²⁴. Women with a history of VTE and those with thrombophilia should not normally be prescribed HRT without expert supervision^{25,26}
- 2 Estrogen and combined HRT regimens are associated with a slight increase in the risk of stroke^{11,27} (approximately 1 additional stroke per 1,000 women per year)
- 3 Recent data suggest that among women aged between 50 and 59 years of age there is a reduced risk of coronary heart disease with estrogen only therapy²⁸. Women starting HRT near the menopause have been shown to have a significantly reduced risk of coronary heart disease²⁹

This consensus statement is based on a combination of clinical experience and scientific evidence and has been produced by an expert panel comprising:

Dr John Stevenson
Dr Diana Mansour
Dr Julie Ayres
Prof Richard Farmer
Ms Elisabeth Hughes
Prof David Purdie
Dr David Sturdee
Mr Malcolm Whitehead

Mr Nick Panay
Dr Farook Al Azzawi
Dr Heather Currie
Dr Sarah Gray
Dr Anthony Parsons
Dr Keith Spowart
Dr Martyn Walling

The preparation of this Consensus statement was funded by an unconditional educational grant from Wyeth. The views expressed in the statement are those solely of the authors and not necessarily those of Wyeth.

August 2006

References

- 1 Notelovitz M, Lenihan JP, McDermott M *et al.* Initial 17 β -Estradiol dose for treating vasomotor symptoms. *Obstet Gynecol* 2000;**95**:726-31.
- 2 Utian WH, Shoupe D, Bachmann G *et al.* Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens and medroxyprogesterone acetate. *Fertil Steril* 2001;**75**:1065-79.
- 3 Lindsay R, Gallagher JC, Kleerekoper M *et al.* Effect of lower doses of conjugated equine estrogens with and without medroxyprogesterone acetate on bone in early postmenopausal women. *JAMA* 2002;**287**:2668-2676.
- 4 Delmas PD, Confavreux E, Garnero P *et al.* A combination of low doses of 17 β -estradiol and norethisterone acetate prevents bone loss and normalizes bone turnover in postmenopausal women. *Osteoporos Int* 2000;**11**:177-187.
- 5 Pickar JH, Yeh I-T, Wheeler JE, *et al.* Endometrial effects of lower doses of conjugated equine estrogens and medroxyprogesterone acetate: two-year substudy results. *Fertil Steril*. 2003;**80**:1234-40.
- 6 Kurman RJ, Félix JC, Archer DF *et al.* Norethindrone acetate and estradiol-induced endometrial hyperplasia. *Obstet Gynecol* 2000;**96**:373-9.
- 7 Jick H, Derby LE, Myers MW, *et al.* Risk of hospital admission for idiopathic venous thromboembolism among users of postmenopausal oestrogens. *Lancet* 1996; 348:**981**-983.
- 8 Grodstein F, Manson JE, Colditz GA *et al.* A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann Int Med* 2000;**133**:933-941
- 9 Cancer Statistics: Registrations Series MBI: Office of National Statistics (ONS) London.
- 10 Bush TL, Whiteman M and Flaws JA. Hormone replacement therapy and breast cancer: A qualitative review. *Obstet Gynecol* 2001;**98**:498-508.
- 11 The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. *JAMA* 2004;**291**:1701-1712.
- 12 Stefanick ML, Anderson GL, Margolis KL, *et al.* Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. *JAMA* 2006;**295**:1647-1657.
- 13 Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52 705 women with breast cancer and 108 411 women without breast cancer. *Lancet* 1997;**350**:1047-1059.
- 14 Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003;**362**:419-27.
- 15 Chlebowski, RT, Hendrix SL, Langer RD *et al.* Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women. The women's health initiative randomized trial. *JAMA* 2003;**289**:3243-3253.
- 16 Borugian M, Sheps S, Kim S *et al.* Waist-to-hip ratio and breast cancer mortality. *Am J Epidemiol* 2003; **158**(10):963-968.
- 17 Morimoto L, White E, Chen Z *et al.* Obesity, body size and risk of postmenopausal breast cancer: the Women's Health Initiative United States. *Cancer Causes and Control* 2002;**13**(8):741-751.
- 18 Al Delaimy WK, Cho E, Chen W, *et al.* A prospective study of smoking and risk of breast cancer in young adult women. *Cancer Epidemiol Biomarkers and Prev* 2004;**13**(3):398-404.
- 19 Manjer J, Johansson R and Lenner P. Smoking is associated with postmenopausal breast cancer in women with high levels of estrogens. *Int J Cancer* 2004;**112**(2):324-328.
- 20 Petri A, Tjonneland A, Gamborg M *et al.* Alcohol intake, type of beverage and risk of breast cancer in pre- and postmenopausal women. *Alcohol Clin Exp Res* 2004;**28**(7):1084-1090.
- 21 Lenz S, Goldberg M, Labroche F *et al.* Association between alcohol consumption and postmenopausal breast cancer: results of a case-control study in Montreal, Quebec, Canada. *Cancer Causes and Control* 2002;**13**(8):701-710.
- 22 Daly, M. P. Vessey, M. M. Hawkins, J. L. Carson, P. Gough, and S. Marsh. Risk of venous thromboembolism in users of hormone replacement therapy. *Lancet*. 348(9033):977-80, 1996.
- 23 Hoibraaten E, Abdelnoor M, and Sandset PM. Hormone replacement therapy with estradiol and risk of venous thromboembolism—a population-based case-control study. *Thromb Haemost*. 1999; **82**(4):1218-21, 1999.
- 24 Scarabin PY, Oger E, Plu-Bureau G; Estrogen and Thromboembolism Risk Study Group. Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. *Lancet*. 2003;**362**(9382):428-32.
- 25 Herrington DM, Vittinghoff E, Howard TD *et al.* Factor V Leiden, hormone replacement therapy, and risk of venous thromboembolic events in women with coronary disease. *Arteriosclerosis, Thromb Vasc Biol*. **22**(6):1012-7..
- 26 Hoibraaten E, Qvigstad E, Arnesen H *et al.* Increased risk of recurrent venous thromboembolism during hormone replacement therapy—results of the randomized, double-blind, placebo-controlled estrogen in venous thromboembolism trial (EVTET). *Thromb & Haemost*.2000;**84**(6):961-7.
- 27 Wassertheil-Smoller S, Hendrix S, Limacher M *et al.* Effect of estrogen plus progestin on stroke in postmenopausal women. *JAMA*;**289**:2673-2684.
- 28 Hsia J, Langer RD, Manson JE *et al.* Conjugated equine estrogens and coronary heart disease. *Arch Intern Med*. 2006;**166**:357-365.
- 29 Grodstein F. Hormone therapy and coronary heart disease: The role of time since menopause and age at hormone initiation. *J of Women's Health*, 2006;**15**(1):35-44.