

2016 IMS Recommendations on Midlife Health MHT: How long? How much? What type?

Paula Briggs

Consultant in Sexual & Reproductive
Health, Southport & Ormskirk Hospital
NHS Trust, UK

“2016 IMS Recommendations on Midlife Health and POI”?

Menopause Hormone Therapy (MHT)

- Background
- How long?
- How much?
- What type?
- What's next?

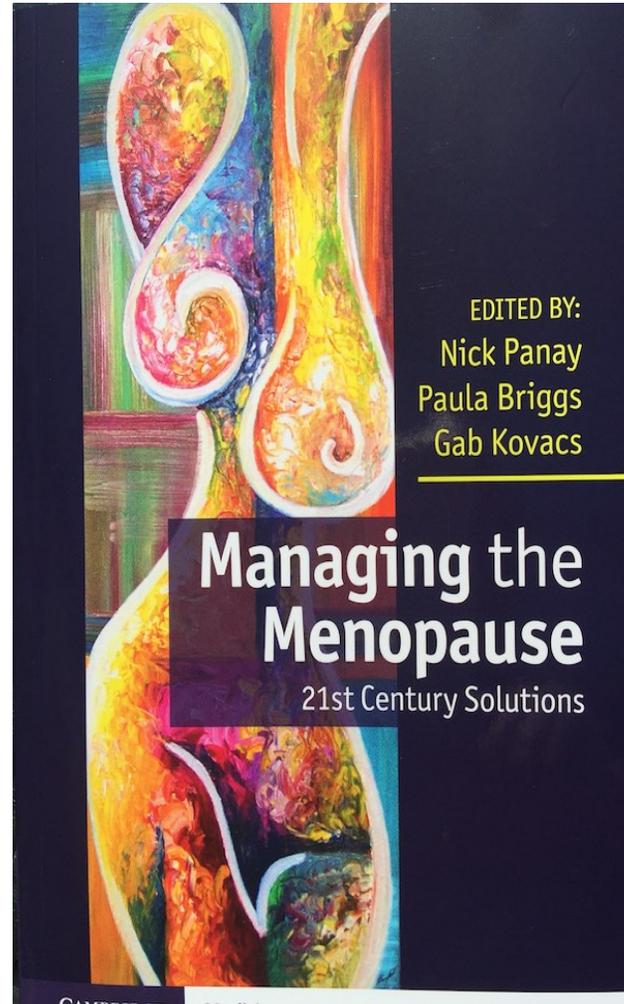
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2016 IMS Recommendations on MHT

- The 2016 revision of the IMS Recommendations
 - published when the atmosphere around the issue of MHT is much more rational
- Recommendations produced by a writing group of experts
 - considered view of the IMS on the principles of MHT in the peri- and postmenopausal periods
- Recommendations now include grading
 - levels of evidence 1 to 4 and some practical 'Good practice points'



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2016 IMS Recommendations on MHT

- Introduction
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Governing principles

Duration of therapy

- **There are no reasons to place mandatory limitations on the duration of MHT**
 - Whether or not to continue therapy should be decided at the discretion of the well-informed woman and her health professional, dependent upon specific goals and an objective estimation of ongoing benefits and risks

Governing principles

Duration of therapy

- Women can have the option of MHT for as long as they derive symptomatic benefit and are aware of the risks for their regimen and personal circumstances
- They can try without MHT every few years, but menopausal symptoms in some women can last for many years and should be treated with the lowest effective dose

2016 MHT Recommendations

Duration - POI

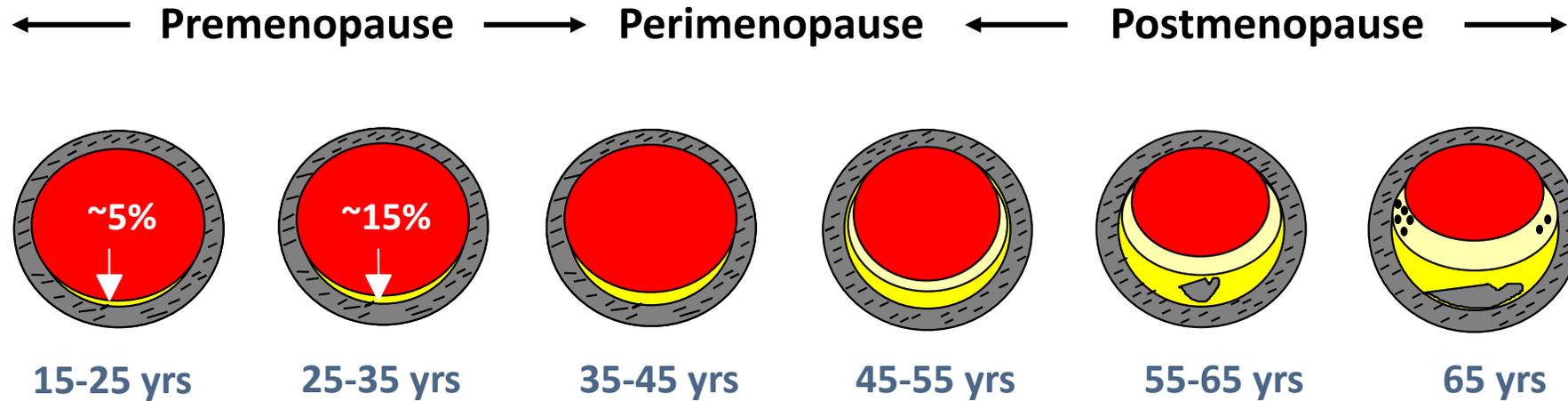
- The mainstay of treatment is estrogen replacement which needs to be continued until the average age of the natural menopause (2)
- Untreated POI increases risk of cardiovascular disease, osteoporosis, cognitive decline, dementia and Parkinsonism (2)

2016 MHT Recommendations

Duration (The window of opportunity) - CHD

- There is evidence that estrogen therapy may be cardioprotective if started around the time of menopause (often referred to as the 'window of opportunity' or 'timing' hypothesis), and may be harmful if started more than 10 years after menopause (1)

Hearts



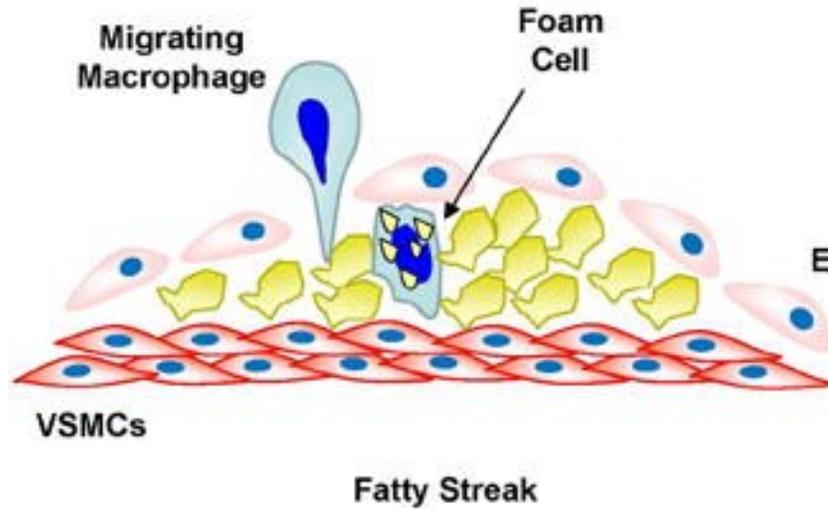
Benefits of Endogenous E₂

Primary Benefits of HT

No Benefits of HT

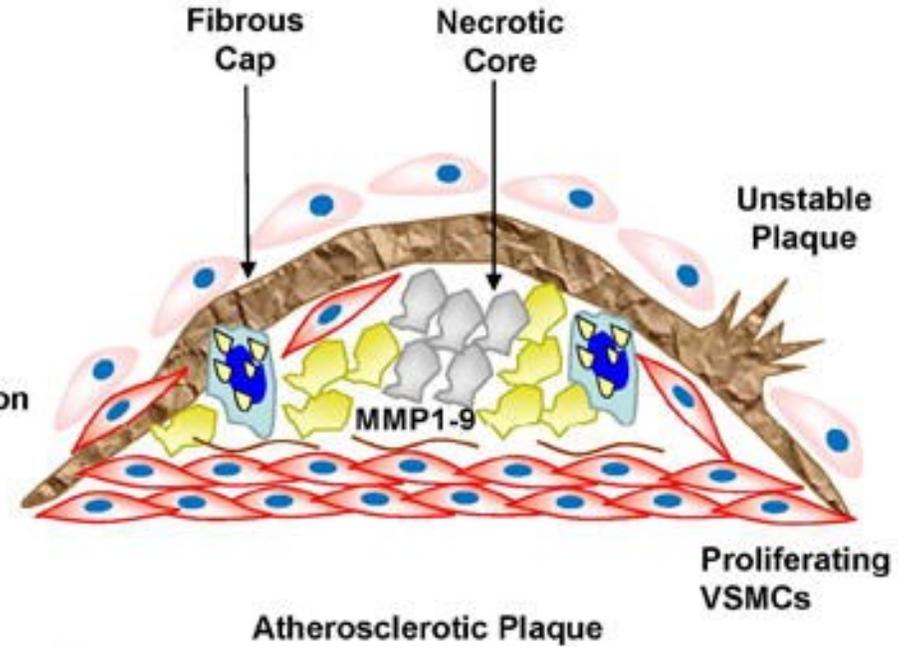
Estrogenic Menopausal Hormone Therapy and Atherosclerosis

Early Atherosclerosis



EC Dysfunction

Established Atherosclerosis



Protective Effects of Estrogenic MHT

Functional ERs

- ↑ Vasodilation: ↑ NO & PGI₂, ↓ ET-1
- ↓ Inflammation: ↓ CAMs, MCP-1, TNF- α
- ↓ VSMC proliferation
- ↓ Platelet activation
- ↓ LDL peroxidation

↓ Lesion Progression

Harmful Effects of Estrogenic MHT

- ↓ ER Expression and Function
- ↓ ER-Mediated Vasodilatation
- ↑ Inflammatory Process
- ↑ MMPs
- ↑ Neovascularization

↑ Plaque instability

2016 MHT Recommendations

Duration (The window of opportunity) - mortality

- Meta-analyses of RCTs, including data from the WHI, have shown a significant reduction in coronary artery disease (CAD) as well as mortality in women treated with oestrogen **under the age of 60** (1)
- In the most recent Cochrane analysis, women **within 10 years of menopause** had a reduction of all-cause mortality of 0.70 (95% CI 0.52–0.95) and of cardiovascular mortality of 0.52 (95% CI 0.29–0.96) (1)

2016 MHT Recommendations

Duration (The window of opportunity) – mortality

- An observational study from Finland recently reported that estradiol products (oral and transdermal), with and without progestogen, decreased coronary and all-cause mortality significantly (12–54%)

2016 MHT Recommendations

Duration - Cognitive Aging (below 60)

- A large three-arm trial of MHT in women below age 60 years showed **no cognitive benefit or harm after mean treatment periods of 4 years** (conjugated estrogens or transdermal estradiol, with cyclical oral progesterone, versus placebo [KEEPS]) (1)
- **Results from small, short-duration clinical trials** in surgically menopausal women suggest that estrogen therapy could be of short-term cognitive benefit when initiated at the time of oophorectomy (1)

2016 MHT Recommendations

Duration - Breast Cancer

- **The possible increased risk of breast cancer associated with MHT is small and estimated at less than 0.1% per annum, or an incidence of < 1.0 per 1000 women per year of use (1)**
- It is similar or lower than the increased risks associated with common lifestyle factors such as reduced physical activity, obesity and alcohol consumption (2)

2016 MHT Recommendations

Duration - Breast Cancer

- Data from the WHI study demonstrated no increased risk in first-time users of MHT during the 5–7 years since initiation of treatment (1)
- The WHI study also demonstrated that 7.1 years of treatment with unopposed CEE **decreased** the risk of breast cancer diagnosis and mortality in hysterectomised women (1)

2016 MHT Recommendations

Duration - Ovarian Cancer

- A meta-analysis of 52 studies claimed that MHT (both estrogen-only and estrogen plus progestogen) increases the risk of ovarian cancer by 1.2–1.4 fold (1 additional case per 5000 w/y)
- Absence of duration/response effect & failure to evaluate dose/response

2016 MHT Recommendations

CLIMACTERIC 2014;17:1-2

Editorial

Vulvovaginal atrophy – a tale of neglect

Nick Panay and Anna Fenton

EDITORS-IN-CHIEF

The impact of vulvovaginal atrophy (VVA) on quality of life continues to be underestimated according to an expert review published in this issue of *Climacteric*¹. The reasons for this are multiple and complex. Women are reluctant to complain about the problem for risk of personal embarrassment and for social and cultural reasons. Health-care providers are reluctant to bring the problem up in consultation because they are uncomfortable discussing sexual issues and for fear of triggering extensive complex dialogue with limited time to deal with the consequences; they also lack knowledge as to the available effective treatment options, both hormonal and non-hormonal. Even though we have an aging population adaptation of a dermatology quality-of-life scale². However, by the admission of the authors of the paper, there is considerable work still to be done. The ultimate goal must be to devise a practical, validated questionnaire which accurately assesses the impact of VVA symptoms on personal, social and professional aspects of quality of life.

Despite guidelines issued by the International Menopause Society and other societies^{4,5}, there continues to be confusion regarding key issues in the use of local estrogen therapy, particularly in primary care. Unfounded concerns are often raised, despite these issues having been clarified by the society recommendations. The most commonly raised concerns include:

- VVA / GSM – Duration
- Treatment should be started early, before irreversible atrophic changes have occurred, and needs to be continued (indefinitely) to maintain the benefits [B]

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Governing principles

Dose

- **Dosage should be titrated to the lowest effective dose**
- **Lower doses of MHT than have been used previously may reduce symptoms sufficiently and maintain quality of life for many women**
- **Long-term data on lower doses re fracture or cancer risks and cardiovascular implications are still lacking**

Consensus: Cardiovascular Disease

- Randomised clinical trials (RCT) and observational data as well as meta-analyses have provided strong evidence that standard dose estrogen alone MHT decreases coronary disease and all cause mortality in women below the age of 60 when commenced within 10 years of menopause
- Data on standard dose estrogen plus progestogen in this population show a similar trend

2016 MHT Recommendations

Dose-Stroke

- The risk of ischemic stroke with MHT is related to oral therapy, with **lower doses having a smaller risk** suggesting a primary thrombotic mechanism (2)
- **Low-dose transdermal estradiol** (\leq / $<$ 50 μg) does not increase the risk of stroke

2016 MHT Recommendations

Dose - POI

- **Women with POI need higher doses of estrogens compared to women over 40 years old (2)**
- The recommended estrogen doses are:
 - 17 β -estradiol PO 2-4 mg/day ,
 - conjugated equine estrogen (CEE) 0.625 – 1.25 mg/day
 - transdermal estradiol 75-100 μ g/day
- Even higher doses may be required in some individuals to fully control symptoms

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Consensus: MHT Type

- Estrogen as a single systemic agent is appropriate in women after hysterectomy
 - additional progestogen is required in the presence of a uterus
- Local low dose estrogen therapy is preferred for women whose symptoms are limited to vaginal dryness or discomfort associated with sexual intercourse
- The use of custom compounded bio-identical hormone therapy is not recommended

2016 MHT Recommendations

Type - POI

- Combined estrogen/progestogen contraceptive pills (COCs) may be used continuously until the expected time of the menopause
 - data are lacking regarding impact on bone and cardiovascular disease
- Data from small randomized trials using surrogate markers suggest that bone mineralization and metabolic effects are more favorable with MHT compared to COCs (1)

2016 MHT Recommendations

Type - VTE

- Oral MHT increases the risk for venous thromboembolism (VTE) (1)
- Transdermal estrogen averts the risk associated with oral MHT and should be considered in higher-risk women (2)

2016 MHT Recommendations

Type -VTE

- The impact on the risk of a thromboembolic event may also be affected by the **type and duration of progestogen**
- Medroxyprogesterone acetate (MPA) may be associated with greater risk when used in oral therapy, as is the use of continuous combined regimens compared with sequential regimens (2)

2016 MHT Recommendations

Type - Breast Cancer

- Three studies suggest that micronized progesterone or dydrogesterone could be associated with a lower risk than synthetic progestogen (2)
- A large European observational study (EPIC) suggested that micronized progesterone or dydrogesterone used in association with oral or percutaneous estradiol may be associated with a better risk profile for breast cancer than synthetic progestogens (2)

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IMS: Governing principles on MHT – Summary

- **The option of MHT is an individual decision in terms of quality of life and health priorities as well as personal risk factors such as age, time since menopause and the risk of thromboembolism, stroke, ischemic heart disease and breast cancer**
- **The dose and duration of MHT should be consistent with treatment goals and should be individualized**
- **MHT is the most effective treatment for moderate to severe menopausal symptoms before the age of 60 years or within 10 years after menopause**

2016 Updated IMS Recommendations: What's Next? Nick Panay's 6 point action plan

- 1) Health Departments & Regulators – Encourage change of policy
- 2) The Prescribers – Expand education and training in menopause
- 3) Media – Engage positively, highlighting favourable data
- 4) Pharma Industry – Reverse negative commercial/R&D decisions
- 5) The Menopausal Woman – Improve her access to information
- 6) HRT – Clarification of differences in action/risk profile