

Risks and Benefits of Menopausal Hormone Therapy

Key points

- For the majority of symptomatic women, the benefits of menopausal hormone therapy (MHT) outweigh the risks.
- Consider the risks and benefits of MHT in the individual prior to commencing treatment.
- Aim to commence MHT within the first 10 years after menopause.
- Consider the use of transdermal preparations to reduce the risk of thromboembolism.
- Micronised progesterone and dydrogesterone may be associated with lower risks compared with other progestogens
- There is no evidence of increased breast cancer risk with the use of vaginal oestrogen.

As medical practitioners, we are well aware of the benefits of MHT for the treatment of menopausal symptoms and maintenance of bone density. However, in discussing this with women, we may find that she is focused on the risks, real or perceived, of the treatment. It is therefore important to be able to discuss the risks and benefits in a way that is understandable to the individual woman.

Historical perspective

- The first major study of MHT was the Nurses' Health Study, an observational study conducted in women aged 30 to 55 years at entry (1). MHT was associated with reduced mortality, particularly that from cardiovascular disease, prompting subsequent randomised controlled trials (RCT).
- The Women's Health Initiative (WHI) involved two RCTs (one using combined MHT and the other oestrogen-only MHT) evaluating the impact of MHT on cancer, cardiovascular disease, and osteoporotic fractures. The RCT of combined MHT was terminated early (July 2002), with reports that MHT increased the risk of venous thromboembolic disease, stroke, breast cancer and myocardial infarction (2, 3).
- In considering the findings of the WHI, it is important to note:
 - The MHT used was oral conjugated equine oestrogen and medroxyprogesterone acetate
 - The average age of women was 63 (age range 50- 79) and the majority were more than 10 years post menopause.

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- The Collaborative Group on Hormonal Factors in Breast Cancer (4) and two nested case control studies (5) reported an increased risk of breast cancer associated with systemic MHT use including oestrogen only. Like the WHI, the majority of MHT preparations used however were older and may not reflect current prescribing practices.
- The US Preventive Services Task Force examined 18 clinical trials and reported health outcomes, with a focus of risks vs benefit for women using MHT (6). It reported reductions in the risk of osteoporotic fractures (44 fewer cases per 10,000-woman years), diabetes (14 few cases per 10,000-woman years) and colon cancer (6 fewer cases per 10,000-woman years) in oestrogen and progestogen users compared to placebo. In oestrogen only users there were 53 less fractures per 10 000-woman years and 19 less cases of diabetes per 10,000-woman years. These findings are similar to that reported in the WHI.

Subsequent analyses have refined and clarified the findings of the WHI. What is currently understood about the risks of MHT?

Breast cancer

- Different progestogens have different risk ratios for breast cancer. Micronized progesterone and dydrogesterone (which has a similar structure to natural progesterone) appear safer than most synthetic progestogens (4,5,7).
- In the recent article describing two nested case control studies, for women prescribed MHT close to the menopause and short-term use (<5 years), there were 3 extra cases per 10,000 women years for oestrogen alone and 9 extra cases per 10,000 women years for oestrogen plus progestogen use (5). (See table below). The risk is increased with longer duration of use, particularly in older women (>age 60). The risk decreased after MHT was ceased. In contrast, long term follow-up of the WHI RCT showed a statistically significant reduction in the incidence of breast cancer in women taking oestrogen alone (8).
- The increased risk of breast cancer associated with a positive family history is the same in both MHT users and non-users (4).
- Obesity increases the risk of breast cancer. MHT use in obese women does not further increase their risk (4).
- More recent studies demonstrated no increased risk of breast cancer with vaginal oestrogen (4,5).

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Extras cases of breast cancer per 10,000 women years for women using MHT compared to never use in two nested case control studies (10).

	Extra cases of breast cancer per 10 000 women years in MHT users vs never user by age group*		
	50-59	60-69	70-79
Oestrogen only			
Recent use 1-5 years	3	4	8
Recent use ≥ 5 years	-	5	8
Oestrogen+progestogen			
Past use 1-5 years	-	2	5
Past use ≥ 5 years	-	5	8
Recent use 1-5 years	9	15	19
Recent use ≥ 5 years	15	29	36

*Risk of adverse drug reaction <10/10,000 is considered 'rare' (9)

MHT and Cardiovascular disease

- In follow up analyses of the WHI, there was no evidence of harm from cardiovascular disease for women commenced on MHT close to the menopause; there was a trend toward reduced risk for these women (10).
- A Cochrane review of MHT and its relationship to cardiovascular risk has concluded that there was no strong evidence for protection or harm from MHT with respect to cardiovascular disease overall (11). Similar to the WHI, for women who start MHT within 10 years post menopause, there was evidence of reduced mortality or protection from coronary heart disease.
- Use of MHT for primary prevention of cardiovascular disease is not recommended.

MHT and thromboembolic disease:

- Transdermal MHT has not been associated with an increase in risk of venous thromboembolic (VTE) disease at doses ≤50mcg/24 hours (12, 13). The effect of higher transdermal doses is less clear but is less when compared to oral oestrogen.
- The absolute risk of VTE on oral MHT is low, of the order of 2-3 per 1,000 women years (compared to 1 per 1,000 women years in non-users). Oral MHT doubles the woman's baseline VTE risk so the absolute risk will be higher in women with co-existing VTE risk factors eg. smoking and/or obesity.

Supporting women in making a decision

- The risks of MHT must be considered in perspective for each woman and balanced against the benefits, particularly the severity of symptoms.
- Management of menopausal symptoms should be tailored to the individual woman to effectively manage her symptoms and minimise risks

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- For some women any extra risk will be unacceptable but others may feel that the benefits outweigh the risks.
- Some women may be unable to take systemic MHT – refer to '[Non-hormonal treatment options for menopausal symptoms](#)' information sheet

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