Menopausal hormone therapy: is there cause for concern?

Although three-quarters of women experience menopausal symptoms, a subset of more than a third of women have moderate to severe symptoms that are frequently debilitating. Hallmark symptoms include hot flushes and night sweats that persist for about 40% of women into their 60s, disturbed sleep, anxiety and low mood, and vulvovaginal atrophy.[1] The negative effect of bothersome vasomotor symptoms on wellbeing is of the same order of magnitude as housing insecurity.[2] Furthermore, having any vasomotor symptoms more than doubles the likelihood of low self-reported work ability.[3] Postmenopausal oestrogen depletion results in bone loss, leading to osteoporosis and fracture risk.[1] Increased intra-abdominal fat and cardiometabolic changes with menopause predispose to cardiovascular disease, cancer, and dementia.[1]

Indisputably menopausal hormone therapy (MHT) alleviates symptoms and can profoundly improve quality of life.[1] Large randomised controlled trials have shown that MHT reduces fractures (even in the absence of osteoporosis), colon cancer, endometrial cancer, and diabetes risk, and that oestrogen-only MHT reduces cardiovascular disease events.[4] Randomised controlled trials have also shown increased venous thrombosis and gall bladder disease risk with oral oestrogen, and a small increase in breast cancer with oestrogen plus medroxyprogesterone acetate (MPA) or norethisterone (NETA). Hence MHT has shifted to predominantly non-oral oestradiol and, when indicated, progesterone or dydrogesterone.[1]

Against this background, a recent observational study from the Collaborative Group on Hormonal Factors in Breast Cancer[5] has triggered a global shockwave of fear among women that MHT causes breast cancer, similar to that generated previously by the sensational reporting of the first publication of the Women's Health Initiative (WHI) study. The false perception that resulted from misreporting of the WHI findings led to thousands of women discontinuing or never commencing therapy. Australian data published in 2015 suggest that only about 11% of perimenopausal and postmenopausal women aged 40–65 years use MHT despite high symptom prevalence.[6] Is this fear justifiable? No.

Data from observational studies can be hypothesis generating but tend to overestimate treatment effects. Hence, randomised trials are essential to confirm or nullify their findings. Use of routinely collected health data without a priori research aims increases the chance of bias. Much of the data included in the recent Collaborative Group analysis[5] was collected during routine health delivery, or relied on participants recalling past treatment and duration of use. Specific characteristics of the included populations—nurses in the Nurses' Health Study[7] or women attending a mammogram being invited to participate in a study of the breast effects of MHT in the Million Women Study[8]—introduce bias. These two studies contributed almost half the included data.[5] Despite the investigators describing their work as worldwide epidemiological evidence, 67% of the prospective data were from two UK databases (unpublished routinely collected general practice health data and the Million Women Study)[8] and 24% were from the USA, with only one study from the southern hemisphere included.

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With acknowledged limitations, analysis of the WHI trials suggested an increased breast cancer risk with conjugated oestrogen–MPA therapy (hazard ratio [HR] 1·24, 95% CI 1·01–1·53), but no increased risk with oestrogen alone (HR 0·79, 0·61–1·02), with treatment durations of 5–7 years.[4] These risks are lower than the two-times increased risk for conjugated oestrogen–MPA therapy and 1·33-times increased risk for oestrogen alone estimates reported in the recent Collaborative Group observational analysis[5] for predominantly similar MHT formulations. This discrepancy is consistent with the expectation that observational findings are tempered by high-quality randomised controlled trials. Follow-up of the 27 347 participants in the WHI trials for 18 years provides the most convincing MHT safety data.[9] With mortality follow-up available for more than 98% of participants and 7489 deaths, all-cause mortality did not differ from placebo for daily conjugated oestrogen–MPA therapy (HR 1·02, 95% CI 0·96–1·08) or for conjugated oestrogen only (0·94, 0·88–1·01).[9] Neither oestrogen alone nor oestrogen–MPA were associated with total cancer mortality, or any specific

cancer mortality, in the intervention or follow-up phases. For women aged 50–59 years at randomisation, pooled data suggested a significantly reduced all-cause mortality with MHT compared with placebo (HR 0·69, 95%CI 0·51–0·94, p=0·01).[9] This finding emphasises the precariousness of observational data and of evaluating any single effect of MHT in isolation, whether the outcome be a benefit or a risk, as the effects are a composite and clinical decisions are made on the basis of overall effects, including quality of life.

Notably, recommended MHT is now substan-tially different from that included in the Collab-orative Group analysis.[5] Nearly all the data for combined oestrogen—progestogen therapy in the analysis pertained to NETA or MPA. The analysis had insufficient power to draw conclusions about the effects of the preferred progestogens, progesterone (only 50 breast cancer cases included) and dydrogesterone (253 cases). The investigators' conclusion that proges-terone was associated with a two-times increased breast cancer risk if used for 5–14 years was based on only 38 breast cancer cases for this duration of use.

A potentially dangerous consequence of misinter-preting observational data in this context is that early (<45 years) or prematurely (<40 years) menopausal women could stop their MHT. 10% of women have early menopause. Thus, the norm for women younger than 45 years is to be premenopausal. Because early or premature menopause is a hormone deficiency state, breast cancer risk is reduced, but the likelihood of osteoporosis, cardiovascular disease, and premature death is increased.[10] Therefore, for women prematurely menopausal, MHT is physiological therapy that restores overall risks, notably the risk of premature death, back to those of premenopausal woman of the same age.[1]

The findings from the Collaborative Group analysis deserve to be better contextualised. In isolation, such reports offer a unidimensional perspective on a multidimensional issue, disregarding the profoundly detrimental effects of oestrogen deficiency symptoms for many women, the negative bone and cardiometabolic consequences of menopause, and the diverse beneficial effects of MHT. Even with the best estimates of benefits and risks, the art of medicine resides in listening to each woman's story and providing care tailored to symptom severity and effect, and each individual's overall benefit-to-risk profile.

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