Menopausal Hormone Therapy: Limited Benefits, Significant Harms

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Recent publications in the medical literature and the popular press misattribute dozens of symptoms to menopause, stressing the health benefits of menopausal hormone therapy while underplaying its risks.[1-11]

The only symptoms unequivocally associated with menopause are hot flashes, vaginal dryness, and night sweats, which can cause sleep disturbances.[12] Other symptoms attributed to menopause, including aches and pains, tiredness, incontinence, and mood disorders, are equally common among older men and more fairly attributed to aging.[13]

Menopausal hormone therapy is effective for vasomotor symptoms and vaginal dryness, but those are the only proven symptomatic benefits.[12] Serious harms, including stroke, pulmonary embolism, gallbladder disease, and increased breast cancer risk are trivialized or ignored in current narratives.

Much of our knowledge about harms and benefits comes from the Women's Health Initiative (WHI), a federally funded, randomized controlled trial (RCT) that remains the largest, longest trial of menopausal hormone therapy. Between 1993 and 1998, the WHI randomized 16,608 women with an intact uterus to placebo or conjugated equine estrogen, 0.625 mg/day, combined with medroxyprogesterone, 2.5 mg/day, (to counter the risk of endometrial cancer) and randomized 10,739 women without a uterus to conjugated equine estrogen, 0.625 mg/day.[14-16]

Both arms of the WHI were stopped early (in 2002 and 2004) because of harm.[15,16] Combined estrogen-progestin increased the risk of invasive breast cancer, pulmonary embolism, stroke, and a global index of harm.[17] Estrogen-only treatment increased the risk of stroke but not breast cancer or pulmonary embolism.[17]

Menopausal hormone therapy use plummeted after the WHI results were reported, and breast cancer rates subsequently dropped dramatically in all countries with registries.[18] The US Preventive Services Task Force report on hormone therapy for preventing chronic illness notes that combined menopausal hormone therapy is associated with 5 excess breast cancers per 1,000 women.[19]

Combined hormone therapy increased gallbladder disease and deaths from lung cancer and doubled the risk of probable dementia among women older than 65 years.[20,21] Estrogen alone increased ovarian cancer incidence and mortality.[22] Overall, the WHI found that an additional 1 in 500 women per year experienced serious harm with combined menopausal hormone therapy.[15]

The WHI study also found benefits of menopausal hormone therapy. Combined therapy reduced risks of hip fracture and endometrial cancer and slightly lowered the risk of diabetes.[17,22,23] Estrogen alone decreased breast cancer incidence at 10- and 20-year follow-up and decreased fracture risk.[17,24]

Critics claim that women in the WHI were too old and too far from menopause, that harms occurred only in older women, and that the findings do not apply to current formulations.[25] However, although the average age was 63 years, 8,833 (32%) of the 27,347 women randomized were in their 50s, making this the largest RCT of menopausal hormone therapy use among women in their 50s.[25] Also, 7,135 (26%) of women were within 10 years of starting menopause.[26]

An analysis of outcomes in women aged 50 to 59 years found greater harm than benefit with combined and estrogen-only menopausal hormone therapy.[17] Although younger women experienced fewer harms than older women, long-term use remained more harmful than beneficial.

The critique that the hormones tested differ from those used today ignores the fact that the WHI tested the same formulations for which benefits were claimed in observational studies. Also the Kronos Early Estrogen Prevention Study (KEEPS) was an RCT that compared placebo to oral conjugated estrogen or transdermal 17β-estradiol with micronized progesterone in 727 recently menopausal women. At 4 years, no benefit was found for cardiovascular health, cognition, or depression.[27,28] Oral estrogen showed mild benefits on 3 of 6 mood scales; transdermal estrogen was not beneficial.[28] Although no serious

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adverse effects were reported, the sample size was inadequate for most adverse events assessed in the WHI (n = 220 taking oral estrogen; n = 211 receiving transdermal 17β-estradiol with micronized progesterone). Micronized progesterone may not mitigate the risk of estrogen-induced endometrial cancer compared with other progestins, but more study is needed to determine which regimen is safest.[29]

Discrepancies between observational studies and RCTs on menopausal hormone therapy have been well explored. Women who chose to take hormones had higher socioeconomic status, had lower blood pressure, exercised more, and smoked less.[30] Thus, hormone use was a marker for lower baseline risk.

Menopausal hormone therapy is not recommended for long-term use or for chronic disease prevention because RCT evidence indicates that harms outweigh benefits (reduced risk of hip fracture and diabetes).[17,20] The 2022 US Preventive Services Task Force statement on menopausal hormone therapy recommends against its use for primary prevention of chronic conditions because of a lack of net benefit.[31]

Menopause is a positive life experience for many women[32] and should not be medicalized. For bothersome vasomotor symptoms, menopausal hormone therapy should be used for the shortest duration possible. In addition, women must be adequately informed about harms.

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