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We still do not know the answers to fundamental questions about menopause

Reassurance about menopausal hormone therapy should not outrun the evidence, says Amani Meaidi

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Menopause care is changing rapidly. After decades of silence on the topic and caution around menopausal hormone therapy, women are talking about their symptoms, clinicians are becoming more willing to treat them, and attitudes towards regulation are changing. But as clinicians become less reluctant to prescribe hormone therapy, we must be careful not to replace this reluctance with reassurance that is stronger than the evidence.

In 2025, the US Food and Drug Administration convened a panel of experts on menopausal hormone therapy and subsequently decided to remove the longstanding so-called black box warning from hormone therapy products.¹ The decision was presented as a correction of warnings that had overstated the risks of these products for many women. Whether some previous risk communication was too broad is an important question, but removing a warning does not resolve the uncertainties underlying that risk.

These uncertainties extend far beyond hormone therapy: we still do not understand menopause well enough. One of the most fundamental questions yet to be answered is why women experience menopause so differently. Some women experience a few transient symptoms, while others develop severe hot flushes, sleep disturbance, genitourinary symptoms, mood changes, and other complaints. These symptoms can profoundly affect their ability to work, to maintain relationships, and to function in everyday life.

Menopause is often discussed as though the explanation for this experience is straightforward: ovarian hormone levels decline, symptoms follow, and replacing those hormones can alleviate them. But the enormous variation between women suggests a much more complex biology.

Hormonal changes clearly matter, but they are unlikely to explain everything. Genetic susceptibility, neurobiological pathways, metabolic health, previous reproductive experiences, psychosocial factors, and other biological processes may all contribute. Yet we still have limited ability to predict who will develop severe menopausal symptoms, who will benefit most from treatment, and why. This heterogeneity matters not only for symptoms and treatment response, but also for treatment safety.

The history of menopausal hormone therapy shows how difficult it is to communicate risk when the evidence is complex. After a study from the Women's Health Initiative raised concerns about an association

between hormone therapy and breast cancer and cardiovascular disease, this potential risk dominated clinical and public discussion, and hormone therapy use fell dramatically.^{2,3} Subsequent research has shown that the balance of benefits and harms is more nuanced, with important differences according to therapy characteristics.⁴ This evidence has challenged some of the fear surrounding hormone therapy use, but should not lead us to conclude that the question of safety has been settled.

Our nationwide study (doi: 10.1136/bmj-2026-10068), published in *The BMJ*, illustrates this point.⁵ We found that current use of oral menopausal hormone therapy containing oestradiol was associated with an increased risk of venous thromboembolism across regimens, doses, durations, and age at treatment initiation. For ischaemic stroke and myocardial infarction, increased risks were confined to oral high dose therapy used for more than one year, whereas we found no increased thrombotic risk with transdermal therapy. These findings do not support describing menopausal hormone therapy as simply safe or unsafe; the results instead suggest that there is no single risk profile for hormone therapy. Risk may depend on the therapy prescribed, the method of use, the dosage, and duration of treatment.

Unanswered questions

We already know that hormone therapy can be highly effective for many women, but we are yet to elucidate the variation in benefits and harms between individuals. Who is most likely to experience substantial benefit? For whom might the balance of benefits and harms be less favourable? And how do age, comorbidities, and underlying risk modify these effects?

These are the questions menopause researchers need to answer next, and doing so requires research designed to capture heterogeneity rather than exploring average treatment effects alone. We need evidence that distinguishes between formulations, doses, and methods of use, while also accounting for the characteristics and baseline risks of the women receiving hormone therapy. Equally importantly, we need to understand why women experience menopause so differently in the first place. Integrating epidemiological research with biological science may help explain this variation, and ultimately allow treatment to become more individualised, effective, and safe, while potentially paving the way for preventing menopausal symptoms before they become debilitating.

We also need to be honest about uncertainty. Regulatory warnings can influence clinical practice for decades, and removal of such warnings can do the same. Both can shape perceptions of treatment, sometimes more powerfully than the underlying evidence. Neither should become a substitute for communicating what we know and what we do not know.

The goal should not be to return to an era in which women were unnecessarily frightened away from effective treatment, but neither should we enter an era in which enthusiasm for menopause care makes uncertainty disappear from the conversation. Women deserve to know when treatment is likely to help, what risks may be relevant to them, and where evidence remains uncertain. Clinicians need the same information, and researchers need to ask more fundamental questions about menopause itself.

Menopause is not simply a period of hormonal deficiency to be corrected: menopause is a major biological transition and potentially an important window into the long term health of women. Understanding why some women are profoundly affected while others are not may ultimately be as important as understanding how best to treat the symptoms.

We have spent decades learning that fear can outrun evidence; we should make sure that reassurance does not do the same.

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