New Analysis of Women's Health Initiative Data Aims to "Clear the Air" Over Menopausal Hormone Therapy

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Public opinion surrounding menopausal hormone therapy is something of a pendulum. Through the 1990s, it had been held, unmoving, at one extreme, Rebecca Thurston, PhD, a menopause researcher and the director of the Center for Women's Biobehavioral Health Research at the University of Pittsburgh, suggests.

The pendulum of public opinion surrounding menopausal hormone therapy has swung in both directions for decades.

"We viewed it like a panacea for all that ailed you," she said. "We thought it would not only treat your hot flashes and help preserve bone density, but it could also prevent heart disease and dementia and make your skin look good and your waistline tight. There was this idea that it was a fountain of youth."

Then, in July 2002, when researchers behind the landmark Women's Health Initiative (WHI) study halted a clinical trial early due to findings published in *JAMA* that hormone therapy increased the risk of heart disease, breast cancer, stroke, and pulmonary embolism, the pendulum swung rapidly in the other direction.

That was when "the world changed for women," said Mary Jane Minkin, MD, a clinical professor in the Department of Obstetrics, Gynecology, and Reproductive Sciences at the Yale University School of Medicine. A practicing gynecologist, she recalls begging her patients not to throw out the estrogen she believed they needed. But panic and confusion led to widespread drops in hormone therapy use, from 22% of women aged 40 years or older in 1999 to less than 5% a decade later according to national survey data. Even after methodological limitations to the study were reported, many clinicians stopped prescribing hormones—including formulations that weren't linked to the adverse outcomes observed in the WHI study. Menopause education screeched to a halt in medical schools and residency programs. Hormone therapy, Thurston recalled, came to be seen as a poison.

For more than 20 years since, that pendulum has continued to swing between those 2 opposing beliefs. For every editorial that highlighted the misinterpreted dangers of hormone therapy, another sang only its overestimated praises.

However, new research seeking to understand ideal candidates for hormone therapy may help to settle this pendulum somewhere in the center.

Analyzing data from the very study that caused such a seismic shift in menopause care, the investigation in *JAMA Internal Medicine* assessed the age-stratified risk of cardiovascular disease due to hormone therapy among postmenopausal women with vasomotor symptoms such as hot flashes or night sweats in the WHI clinical trials.

The Timing Hypothesis

The primary purpose of the original WHI trials—which studied more than 27 000 postmenopausal women aged 50 to 79 years from 40 clinical centers around the US—was to investigate the potential cardioprotective effects of hormone therapy. Just 2 years after the first trial, a study of estrogen plus progestin therapy, was abruptly stopped, the second trial, on estrogen-only therapy, also ended prematurely. This time, the trial was halted because the intervention increased stroke risk with no demonstrated benefit for heart disease prevention.

Since then, the initiative's own investigators and independent researchers alike have published thousands of scientific articles using data from the WHI.

The new study, a secondary analysis of data from the original trials, asks whether the subset of participants who had vasomotor symptoms were able to treat them safely and effectively with hormone therapy—and whether these outcomes would differ with age. Although prior evidence has suggested age as a key factor in cardiovascular risk with hormone therapy, a specific focus on women with vasomotor symptoms intrigued Jacques Rossouw, MD, an

epidemiologist who was involved in both the new analysis and the original WHI research, which began in the early ’90s and remains the largest women’s health study in the US to date.

The relationship between hormone therapy, cardiovascular disease risk, and vasomotor symptoms, he said, is one “we haven’t studied extensively before” yet is a common clinical question. Up to 80% of women in the US experience vasomotor symptoms during menopause, and they report 4 to 5 hot flashes per day on average. “These symptoms can be so severe that they interfere with daily life and can make women miserable,” said Rossouw, the lead author of the current study. What’s more, growing research has linked vasomotor symptoms with an unfavorable cardiovascular risk profile.

The new analysis of the WHI data found that hormone therapy not only relieved moderate and severe vasomotor symptoms, but it did so without raising the risk of atherosclerotic cardiovascular disease—including nonfatal myocardial infarction, stroke, and peripheral arterial disease—among women aged 50 to 59 years.

By and large, Rossouw said, “these women are not currently receiving hormone therapy, and from our results, it’s justifiable that they should be.”

But back in 2002, Rossouw, then acting director of the WHI, was among those who spoke at a now-infamous press conference that featured what has been described as a “melodramatic presentation” that overgeneralized findings and overemphasized relative risks instead of absolute numbers. Now, he said, “we hope to clear the air in saying that, in younger women with vasomotor symptoms, these hormone therapies do work.”

The same cannot be said for women in their 70s. In this population, the new analysis found that the cardiovascular disease risk did increase with hormone therapy. Plus, for those women receiving the estrogen plus progestin combination, increasing age was linked with diminishing symptom relief.

Overall, the study’s results align with current guidelines for treatment of vasomotor symptoms with hormone therapy in younger postmenopausal women but “underscore the need to avoid” hormone therapy in women after age 70 years, the authors concluded. (An accompanying editor’s note in *JAMA Internal Medicine* added that this updated analysis “provides the best available evidence” on hormone therapy usage for vasomotor symptoms in different ages.)

JoAnn Manson, MD, DrPH, a professor of medicine at Harvard Medical School who was a principal investigator on the initial WHI trials and coauthored the updated analysis, has been researching this “timing hypothesis” ever since the 2002 pendulum swing and publishing reviews of WHI data that more closely align with these new age-stratified findings.

“We are still learning so much from WHI, and I think now we have a refined, deeper understanding that is more nuanced,” said Manson, who continues to serve as a principal investigator for one of WHI’s regional centers and is also chief of the division of preventive medicine at Brigham and Women’s Hospital.

She noted that the vast majority of women who are seeing their clinicians about hot flashes are younger than 60 years or within 10 years of onset of menopause and will respond well to hormone therapy. Meanwhile, Manson said those in their 70s should “think twice” because on top of the “2- to 3-fold increase in cardiovascular disease risk, the hormones may not be effective.”

The study’s authors recommend that women in their 60s should proceed cautiously if initiating hormone therapy. Although there wasn’t a clear signal of harm in this age group, the cardiovascular risks increased with age. “They are probably reasonable candidates, but it’s a very individual decision,” Manson said of prescribing to this population.

“We have a tendency to try to find a one-size-fits-all answer, and hormone therapy is one of the best examples of where one-size-fits-all answers do not work and lead to harmful decision making,” she added.

Adding to that nuance is the fact that the study only addressed the start of treatment, not its continuation or duration. This is an area of continued debate among experts, including those at a recent US Food and Drug Administration (FDA) panel on menopausal hormone therapy. The Menopause Society has stated that continuing hormone therapy beyond age 65 years “is a reasonable option with appropriate counseling and regular assessment of risks and benefits.” Manson also said it’s no longer recommended that women should stop hormone therapy at a “magic age,” particularly if they have continued symptoms and are responding well to treatment.

Rossouw remains skeptical.

"If you start and treat women for a short-term, the risks are very low and there may be some benefits, but if you start and continue, continuing to have benefits is unproven and unprovable" without a trial spanning decades, he said.

The study's treatment period was 5 to 7 years, but a "sizable minority" of women experience vasomotor symptoms well into their 60s and 70s.

"Hot flashes can go on much longer than we previously saw," Thurston said. "What are we going to do for those women?"

WHI's Limitations

The new analysis has other limitations. The original WHI study was open to women in their 50s through 70s, regardless of their menopausal symptoms, Rossouw noted. Although it tracked participants' vasomotor symptoms if they had them, it was not specifically designed to address hot flashes.

Because of that, some sample sizes were quite small, Thurston said, noting that of about 3500 participants in their 70s using combination hormone therapy in the trials, only 172 had moderate or severe vasomotor symptoms at enrollment. "We just have to exercise caution when we interpret them," she said.

The analysis also was not able to consider other menopausal symptoms women experience, which "far transcend vasomotor symptoms," Thurston said. "There's also a whole other panoply of them."

More than half of menopausal women may have sleep problems, often irrespective of hot flashes. Genitourinary symptoms can occur. And women also commonly report mood changes and cognitive symptoms like forgetfulness and brain fog, Thurston said.

But perhaps the most notable constraint was the very hormone therapies used in the trials. The WHI studied 2 oral options: estrogen plus a synthetic progestin for women with a uterus and oral conjugated equine estrogens alone for women who had had a hysterectomy. Both formulations were commonly used at the time the study was designed, roughly 30 years ago, but lower doses and different modalities have emerged since then. For instance, a bioidentical form of progesterone, such as oral micronized progesterone, may have a better safety profile and fewer negative adverse effects than synthetic progestins. Transdermal therapy, in which patches or gels deliver hormones through the skin, are "much less hazardous," Minkin said, in part because they bypass the liver.

"A lot of case control studies show that physiologically, it makes sense that transdermal will not have the clotting risk oral estrogens have," she said.

Rossouw, who served as the project officer for the WHI program at the National Heart, Lung, and Blood Institute from 1993 to 2014, thinks a next-generation WHI study of newer treatments is highly unlikely. "Sadly, it's not feasible to do a trial anymore because of the history of hormone therapy to which we've contributed," he said. "But the reality is that I don't see anybody funding a new trial of hormone therapy."

Minken noted: "A lot of drug companies were burned by the WHI, so who's going to support it?"

Not only has women's health research historically been underfunded, but scientists don't consider menopause—which is experienced by the overwhelming majority of women at some point in their lives—in 99% of preclinical studies of the biology of aging.

Still, Rachel Rubin, MD, an assistant clinical professor of urology at Georgetown University Hospital, called for more up-to-date, relevant research.

"We should absolutely be doing more studies on women who are new into menopause using the therapies that we use now," said Rubin, a sexual medicine specialist. "I don't use the hormone therapy used in the Women's Health Initiative. So the question becomes, can I extrapolate any of this data on the hormone therapy that I do use? That's the challenge."

Then there are other nonhormonal remedies to consider, such as fezolinetant, an oral medication specifically approved by the FDA to treat hot flashes, and selective serotonin reuptake inhibitors, which may improve vasomotor symptoms, sleep, and mood disturbances. The investigational drug elinzanetant, a dual neurokinin-targeted therapy, also shows promise as a potential treatment for moderate to severe hot flashes.

Hormone therapy "can't be the only thing we offer menopausal women," said Thurston. "There absolutely needs to be more innovation in this space. We can't just leave women with this one choice…They no longer need to endure."

What's Next?

Minkin believes the new study will be a service to clinicians struggling with how to navigate their patients' menopausal symptoms.

"The WHI release essentially destroyed menopause education in the US," she said. "A whole generation of practitioners out there, people who have trained throughout the past 20 years, don't know what to do."

Addressing curriculum and training should be a top priority, Rubin added, and not just for obstetrics and gynecology physicians. "Every clinician who takes care of women should know the benefits of hormone therapy."

A 2017 survey of medical residents showed that only 6.8% felt adequately prepared to manage patients experiencing menopause. Hormone therapy is "tremendously complex," Manson noted, and the knowledge gaps have only "gotten worse as the years go by" with patients paying the price.

Thurston has observed women seeking medical advice from online influencers, many of whom promote supplements or unapproved treatments for menopausal symptoms. She considers it "completely understandable" when there's a dearth of evidence-based expertise.

She advises clinicians to complete thorough evaluations of their patients' medical and family histories, symptoms, contraindications, and "own set of priorities in terms of what really matters most" to them in their menopause journey. "These do need to happen in a one-on-one conversation," she said. "There's not easy blanket advice."

The pendulum, according to Manson, seems to be settling in the right spot.

"It's a matter of identifying the appropriate candidates who will have a favorable risk-benefit profile and distinguish them from those who won't," she said. "If you're going to say hormone therapy is good for all women or it's bad for all women, either conclusion is off base and will end up harming all women, by either giving them a treatment they don't benefit from or denying treatment to women who would benefit."

Minkin has been experiencing the effects first-hand.

"What is happening now is women—hundreds of women in my practice—who are going through perimenopause and menopause are saying, 'Wait a minute, I need estrogen therapy,'" Minkin said, adding that "many dozens of women who are much older" tell her they were robbed of it when they needed it most.

Rubin added: "We've been scaring women for over 20 years. This research just continues to reassure us that we must move past [the original WHI trials] and really treat women with menopausal symptoms. It continues to reinforce that hormone therapy is not as scary as once believed."

Article Information

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