the estrogen Question

HORMONE THERAPY MAY PREVENT DEMENTIA AND IMPROVE CARDIOVASCULAR HEALTH, BUT ARE THE DANGERS TOO GREAT?

by Elisabeth Andrews

Can estrogen therapy protect women against cognitive decline? A growing body of research shows that the hormone, once thought to be solely for reproduction, plays a critical role in cognition. It appears to be particularly crucial to verbal memory and learning, tasks that become increasingly difficult with age. Researchers are now trying to determine whether estrogen replacement therapy initiated at the onset of menopause could prevent or delay the expression of dementia later in life. There is evidence to support the theory, but is it enough?

In terms of the brain's structure, estrogen clearly has a cognitive role. Estrogen receptors have been identified throughout the brain, with concentrations in areas related to memory, like the hippocampus and cerebral cortex. Tissue cultures show that estrogen has a number of beneficial effects on neurons, such as protecting against toxins and aiding the synthesis, metabolism and release of neurotransmitters, neuropeptides and neurosteroids. Estrogen also appears to increase blood flow to the brain.

When animals are given estrogen as part of a research study, they tend to exhibit better brain function compared to those that are deprived of the hormone. But when it comes to studies of people, the data is less clear. →

To understand why there is such uncertainty, it helps to know a little history of estrogen therapy. Women's estrogen levels drop precipitously during the transition to menopause, contributing to symptoms like hot flashes and night sweats. Estrogen therapy has been widely prescribed to manage these menopause symptoms since the 1960s. In the '70s, it became clear that taking estrogen increased the risk of endometrial cancer. Adding progesterone (another reproductive hormone, called a "progestin" when synthetically altered for pharmaceutical purposes) eliminated that excess risk.

In the ensuing decades, several "observational" studies looked at women who were taking hormone treatment and identified a number of additional benefits they appeared to be enjoying: stronger bones, better cardiovascular health and a reduced risk of developing Alzheimer's disease.

The problem with those findings was that they applied only to women who had voluntarily begun taking the treatment. It wasn't clear whether those women represented the larger population or whether they were unusually healthy people who had begun hormone treatment as a means to maximize their well-being.

To address this question, a large national study called the Women's Health Initiative (WHI) randomly divided more than 160,000 postmenopausal women into groups who would receive either hormone treatment or a placebo. Researchers hoped to track potential benefits to bone, heart and brain health. But what the study began to reveal was surprisingly, even shockingly, bad.

It became clear that study subjects taking a combination of estrogen and a progestin had more strokes, more cardiovascular events and more breast cancer. The researchers discontinued that portion of the trial in 2002, and estrogen's popularity took a nosedive. Fears were further heightened when data from that same group showed twice the rate of dementia among women taking the hormone therapy.

The flurry of bad press caused a "mass exodus away from hormone therapy," recalls Dr. Daniel Cosgrove, who directs a preventive medicine clinic in California. "Before that, the trend was all pro-hormone, then the WHI jolted everyone and the pendulum swung back."

But the public reaction to the event, he says, drastically oversimplified what was revealed through the WHI. By looking collectively at postmenopausal women ranging in age from 50–79 years, the study grouped together two very different sets of people—those who were newly menopausal, and those who hadn't menstruated for more than 10 years. Also, the negative results pertained specifically to the use of a brand-name drug called Prempro, made with a progestin called medroxyprogesterone (MPA, brand name Provera). Essentially, he says, the study gave the wrong people the wrong hormones.

"They discontinued the trial because 'women on hormones' were having more strokes and heart disease," he says. "But it was older people who were suddenly started on Prempro. That's very different from women who are 49 and having hardly any periods shoring up with estrogen."

In fact, a different branch of the WHI study found that women who were given estrogen without a progestin (because those women had hysterectomies and were not susceptible to endometrial cancer) actually had lower rates of breast cancer than women taking a placebo. Moreover, when women who were 50–59 years old at the start of the estrogen trial were looked at separately from older women, researchers found they had much lower rates of heart disease. In a follow-up report in 2007, the WHI study authors concluded that the effects of hormone therapy on heart disease varied according to how long it had been since the user had gone through menopause.

A part of the WHI called the Women's Health Initiative Memory Study (WHIMS) found that estrogen alone increased the risk of dementia—but the women in that study were all over 65. The cognitive question couldn't be addressed directly with the group of younger women, because dementia is so rare in women under 60.

Notably, the study found an increased risk of stroke but a reduced risk of hip fractures for both types of therapy across all age groups.

Because the WHI showed so many negative effects for the women as a whole, the American College of Obstetricians and Gynecologists took the position that hormone therapy should be used only to treat severe symptoms of menopause, not as a means of preventing heart disease or cognitive decline, and that it should be used for as short a time and at as low a dose as possible.

Dr. Elizabeth Barrett-Connor, division chief of epidemiology at the University of California San Diego School of Medicine and the principal investigator on a number of clinical trials involving hormone treatment, explains her cautious approach: "I think the question may still be open, but I could not with good conscience recommend estrogen to a woman who was not miserable [from menopause symptoms] in hopes of improving her memory as a side benefit. The data just do not show this."

Unfortunately, there may never be data showing definitively that taking estrogen therapy at the time of menopause reduces the risk of dementia in later life. There's just no way to conduct the study that would prove it, says Dr. Pauline Maki, a professor of psychiatry and psychology at the University of Illinois at Chicago. "You'd have to get a few thousand women in their late 40s and early 50s, randomize half of them to hormone therapy, and then follow them for 20 or 30 years. Who's going to fund that study?"

Dr. Maki, whose research focuses on the effects of sex hormones on the brain, is one of a number of researchers who think the evidence is mounting for a neuroprotective role of estrogen therapy when taken during menopause. Putting everything together—the biological pathways, the observational studies, the WHI data, and findings from a number of small studies on younger women that suggest that hormone therapy could improve verbal memory—Dr. Maki says it looks like there is a "critical window" during which estrogen therapy could have a beneficial effect on cognition.

"One of the reigning perspectives in the field is something called the *critical period hypothesis*," she explains. "That hypothesis states that the effects of estrogen have to do with the timing of the therapy. It's based on the idea that there is some evidence to suggest that initiating hormone therapy early in the menopausal period might lead to neuroprotection, whereas initiation later in life may have detrimental effects."

What the study began to reveal was surprisingly, even shockingly, bad.

Dr. Stanley Birge is another proponent of the critical period hypothesis. A professor of geriatrics and nutritional science at the Washington University School of Medicine in St. Louis, he's convinced that estrogen therapy has the potential to substantially reduce the risk of heart disease and dementia—but only if it's taken early on.

"What we think happens at the time of menopause is that it initiates a cascade of events that ultimately results in the expression of Alzheimer's," he says. "Starting hormone therapy after that cascade has been initiated is not going to prevent that progression."

While there's little chance of a 30-year clinical trial settling the question, Dr. Maki says that researchers are looking at "proxy markers" to point toward estrogen's potential cognitive benefits.

For example, a large body of research links risk factors for cardiovascular disease with the risk of developing dementia. Two major studies are now underway that will look at the effects of estrogen therapy initiated at the time of menopause on hardening of the arteries, a major risk factor for heart attacks. If the studies can show that estrogen therapy reduces the risk of cardiovascular disease, it could wind up being used to prevent dementia as well, because, as Dr. Maki says, "Guidelines recommend controlling cardiovascular risk factors as a way of lowering dementia risk." → 65

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Neuroimaging is another strategy for indirectly assessing estrogen's potential for preventing dementia. Researchers have begun to use technologies like magnetic resonance imaging (MRI) and positron emission tomography (PET) to view the effects of estrogen on brain activity. So far, these scans appear to show increased activity in the hippocampus and frontal cortex in response to estrogen, suggesting enhanced memory function.

The neuroimaging findings seem to fit with those from another form of proxy investigation: short-term studies of estrogen's effects on verbal memory. Dr. Maki describes a test in which women study a grocery list and are then asked to recall the items on the list 20 minutes later.

"This ability to remember items after a delay—'delayed memory'—is the strongest predictor of dementia," she explains.

Although her reviews of this type of research find evidence for a beneficial effect of estrogen on verbal memory and attention, she explains that changes in memory capabilities are notoriously difficult to detect. "It's very difficult to measure changes, because if I study your memory today, next time you will improve on those tests. You may have developed some smart strategies to use next time around. The fact that I've measured your memory before, changes the results."

This "testing effect" is not the only obstacle to assessing memory in younger menopausal women. Dr. Birge explains that although many women complain of memory impairment around the time of menopause, the current assessment tools are not adequate to measure those types of changes. "It's very hard to measure cognitive function in a healthy individual," he says. "Women will tell you, 'I'm not the same. I am really struggling,' but our tests don't have that sensitivity. They are designed to detect dementia."

Further complicating the issue is the difficulty of measuring women's estrogen levels. For one thing, levels fluctuate significantly over time. But another problem is that most circulating estrogen is bound to a type of protein that prevents it from crossing the blood-brain barrier.

"Research shows that the correlation between blood levels and brain levels of estrogen is only moderate," says Dr. Maki. Even if researchers can get an accurate idea of a woman's circulating estrogen level, it's hard to tell how much of it is affecting her brain.

Finally, even if the evidence does eventually add up to a recommendation that estrogen be used to preserve cognitive function, there are still the issues of stroke and endometrial cancer. The most current research is focused on ways to reduce these risks without compromising the effectiveness of estrogen therapy.

With respect to stroke, it appears that taking oral estrogen stimulates the liver to produce not only the proteins that bind to the hormone, but also, in some women, very similar proteins that instead cause blood clots. One potential solution to the problem is delivering estrogen through a skin patch—transdermal estrogen—in order to bypass the liver.

As for endometrial cancer, the risk is reduced with progesterone, but the WHI and many other studies suggest that MPA, the most common type of progestin, also blocks estrogen's beneficial effects for the heart and brain. The new frontier in addressing this roadblock is the development of SERMs—selective estrogen receptor modulators. These compounds are designed to block estrogen receptors in specific areas such as the uterus, while allowing the hormone to still reach other regions such as the heart, brain and bones.

So, while there is much evidence for estrogen's potential to protect cognition, both through direct effects and indirectly through improved cardiovascular health, there is still a great deal of research underway to determine precisely how women could benefit and the best way to minimize risks associated with the treatment.

For now, Dr. Maki says it's helpful to think of the "woman on the street" to understand what the research tells us.

"Let's say you have a woman who is going through menopause and is highly symptomatic, and she's being advised to take hormone therapy for about five years and then taper off. What does the research say about her? With the exception of the combination with MPA, other forms of hormone therapy seems sufficient to delay the onset of Alzheimer's disease. The wealth of the evidence shows that five years of hormone therapy is at least safe and potentially beneficial for cognitive function." **[bw]**

our hormones...

Another important hormone produced in the brain by the pituitary gland is antidiuretic hormone, also known as ADH. It controls the body's water metabolism. As Dr. Litofsky explains, if a person loses a lot of blood, the brain realizes that and sends ADH as a signal to the kidney to hold onto fluid. Or if a person becomes dehydrated, the brain detects too much salt in the blood and tells the pituitary gland to send ADH.

The pituitary gland also produces human growth hormone, which is sent to the liver to stimulate the production of insulin-like growth factor. This travels to the tissue and aids in growth. Human growth hormone has been abused by athletes and some doctors try to sell it as a "fountain of youth" tonic, capable of fixing a long list of ailments. The pituitary also produces thyroid-stimulating hormone, which stimulates the thyroid to produce the hormones that are responsible for our metabolism in general.

Steroids, like human growth hormone, are also misused by athletes. Just ask any major league baseball player. To enhance performance, athletes can use testosterone, a hormone produced by the testes in men and the ovaries in women. Steroids help an athlete build muscle more quickly and might help quicken recovery from tough workouts. But the quick fix comes at a high price. Steroid use can cause a host of negative repercussions including depression, aggression and tumors.

While both men and women have the same hormones, they produce them in different quantities, and some don't have much to do with body function. From menstruation to menopause, it seems like when it comes to hormones, women have more to worry about. "They have more cyclical patterns that require regulation than men do," Dr. Litofsky says. But, the reason for worry might not be all scientific. "It may be that men don't talk about their hormone-related issues."

The bottom line is that the human body is complex, and hormones relay important information from the brain to keep it working. "We're not static beings, and things change from moment to moment," Dr. Litofsky says. "The body needs to adapt to those changes, and that's how hormones help us." **[bw]**