WSJ.com THE WALL STREET JOURNAL. ONLINE

July 9, 2007

How NIH Misread Hormone Study in 2002

By TARA PARKER-POPE

On July 9, 2002, federal government health officials announced that they had halted a major study of menopause hormones, saying the drugs increased a woman's risk of heart attack by 29%.

But in the five years since, it's become clear that some aspects of what was initially reported from the $725 million Women's Health Initiative study were either misleading or just wrong. Although the government initially said the findings applied to all women, regardless of age or health status, additional data published in recent months show that the age of a woman and the timing of hormone use dramatically changes the risk and benefits. WHI data published in April in the *Journal of the American Medical Association* showed that women in their 50s who took a combination of estrogen and progestin or estrogen alone had a 30% lower risk of dying than women who didn't take hormones.

Last month, the New England Journal of Medicine reported that 50-59-year-old women in the WHI who regularly used estrogen alone showed a 60% lower risk for severe coronary artery calcium, an important risk factor for heart attack.

How could the heart risks of menopause hormones for this crucial cohort change so dramatically in just five years? Officials from the National Institutes of Health, which directed the study of more than 27,000 women, say the interpretation of the WHI has simply evolved as researchers have used different methods to analyze the voluminous body of data.

The average age of women in the study was 63. While older women in the study did show a heart risk, researchers eventually focused on women in their 50s who were closer to menopause, finding that hormones were more likely to protect those women's hearts than harm them.

But critics including some of the WHI's own investigators, speaking out for the first time, say that NIH officials initially over generalized in large part because they excluded many of the study's own investigators and physicians from the first review. As a result, key questions that could have clarified the data far sooner weren't asked.

Just 11 days before the public announcement in July 2002, the WHI's 40 investigators met in Chicago, where they were told the study had been stopped early. Several people who attended the meeting say several WHI researchers were stunned and angry when they were given final page proofs of the study report for the Journal of the American Medical Association. Although some researchers expressed concern that the results were too broadly interpreted, it was too late to make meaningful changes to the JAMA article. Many investigators who had spent nearly a decade working on the WHI had no input in the final and most important paper.

"I think that had the initial report been written by a broader group, as almost all of our later papers have been, it would have been framed differently," says Robert D. Langer, the former principal investigator for the WHI's clinical center at University of California, San Diego, who was among those who protested at the time. He has since served as an expert witness for hormone maker **Wyeth**. Dr. Langer says he remains concerned that the interpretation of the WHI has unnecessarily scared a generation of women from the treatment.

Jacques Rossouw, a physician with the National Heart Lung and Blood Institute who has overseen the WHI since its inception, confirms that some investigators were upset that they weren't included in writing the first WHI report. "That was an NIH decision supported by the WHI executive committee to keep it to a small group because we realized it was a sensitive paper," he says.

Still, he defends the government's handling of the study results "based on what we knew at the time," and says that study officials wanted to make a dramatic statement. "Our main job at the time was to turn around the prevailing notion that hormones would be useful for long-term prevention of heart disease," he says. "That was our objective. That was a worthy objective which we achieved."

But many in the medical community disagree, saying key questions about long-term use still aren't answered. Although the WHI data clearly shows that starting hormones at an older age is risky, what's not clear is whether the heart protection women get starting at a younger age will continue with long-term use.

That was the question that the WHI was supposed to answer when it was launched in 1991 after data from an ongoing trial of nurses showed that women who used menopause hormones have as much as a 50% lower risk of heart attack. But the WHI designers didn't take into account that the timing of hormone use might affect the results and recruited mostly older, symptom-free women. Some of the study participants were already 20 years past menopause when the WHI began.

Since mostly older women were recruited, there weren't enough recently menopausal women under 60 to generate conclusive data in some of the findings. But the trends were provocative. Among recently menopausal women who used estrogen and progestin, heart attack risk fell 11%. By comparison, women who started taking hormones 10 or more years past menopause had a 22% to 71% higher risk of heart problems.

In a second part of the study, in which women who had undergone hysterectomy took estrogen without progestin, women who started hormones after the age of 70 had an 11% higher risk of heart problems. But women below 60 in the estrogen-only study had a 37% lower heart risk.

In a bid to draw a more definitive conclusion, the WHI in April 2007 published a report in JAMA combining the data from both hormone trials. That paper showed that the timing of hormone use matters: Younger women appear to receive heart protection, while older women are at risk.

"We now have a refined understanding of the benefits and risks of hormone therapy, and there has been so much reassuring evidence for younger women over the last few years," says Harvard professor and WHI investigator JoAnn Manson, who has no ties to drug firms.

Despite the recent data, questions about long-term use of hormones are far from resolved. While most people now agree that hormones are a reasonable option for women to treat menopause symptoms like hot flashes, the bigger question is whether hormones should be considered in the armamentarium of drugs used for heart protection, along with blood pressure medications and cholesterol-lowering drugs called statins.

The National Heart, Lung and Blood Institute, which oversaw the WHI, firmly believes that menopause hormones shouldn't be used to prevent heart disease because of potential risk of blood clot, stroke and breast cancer.

Indeed, the WHI showed that hormones have a range of risks and benefits. On the plus side, they may protect younger women's hearts, they definitely protect against hip fractures, they lower the risk for diabetes and may lower the risk for colon cancer.

On the other hand, menopause hormones do increase the risk for blood clots and stroke. Women in the WHI who used both estrogen and progestin were at 24% higher risk for breast cancer. But women who regularly use estrogen without progestin had a 33% lower risk of breast cancer.

"Hormone therapy long term has these other adverse events hanging around. It doesn't fit the paradigm of what you are looking for in a viable long-term prevention strategy," says Dr. Rossouw. "If you're going to use something to prevent atherosclerosis, your choice is statins, not hormones."

The data on women who use statins are mixed, but suggest that they lower a woman's heart risk by 15% to 20%. Statins carry their own risks, including liver effects, muscle pain, memory problems and in rare cases a life-threatening muscle disease called rhabdomyolysis. There are no studies showing the risks and benefits of long-term use of statins.

Many doctors now believe that for younger women without a uterus, estrogen should be an option for long-term prevention of heart disease. (The progestin is added to protect against uterine cancer.)

"If this is preventing heart disease and saving lives, I think it's really wrong not to consider it," says Yale associate professor Hugh Taylor, a principal investigator for the Kronos Early Estrogen and Prevention Study (KEEPS), a study of estrogen and heart disease funded by Arizona billionaire John Sperling, an education entrepreneur who was upset with the way the WHI study was initially interpreted. "Some of the other drugs we use for cardiovascular disease don't have the evidence that we have for hormone therapy."

Two important ongoing studies will further illuminate the role estrogen plays in heart disease. The KEEPS study is recruiting 720 women, ages 42 to 58, to study the effects of oral or transdermal estrogen as well as progesterone on the coronary arteries of healthy women. An NIH-funded Early Versus Late Intervention Trial will study 500 women and the effects of hormone therapy given within six years of menopause compared to treatment given 10 or more years after menopause. Both studies will also test whether using natural progesterone, instead of the synthetic progestin used in the WHI, lowers or eliminates the risk of breast cancer associated with combination therapy.

Even though the long-term heart issue is unresolved, some critics say the NIH's handling of the WHI data scared away younger women who might want to use hormones for menopause symptoms. "We've gone to considerable efforts to reassure women and gynecologists that it's okay [to use hormones] in the short term," to treat the symptoms of menopause, Dr. Rossouw says.

Still, since the WHI results were announced in 2002, hormone sales have plummeted 30% to $1.9 billion, according to IMS Health, a health-care information company.

"I don't think it's fair to extrapolate from the data that women should be put on this as a preventative treatment for heart disease," says Michael E. Mendelsohn, a Tufts University professor who recently wrote an NEJM editorial about estrogen and heart disease. "What the data does support is that women who use hormones to treat menopause symptoms can feel reassured that they are not increasing their cardiovascular risk and may be providing some long-term benefit."

Write to Tara Parker-Pope at tara.parker-pope@wsj.com1

Corrections & Amplifications:
The Women's Health Initiative clinical trials were designed to answer many questions, including whether starting hormones between the ages of 50 and 79 would lower the risk of heart disease in women. This article incorrectly says the WHI intended to address only whether the heart protection women get from taking hormones at a younger age continues with long-term use.

URL for this article:
http://online.wsj.com/article/SB118394176612760522.html
Hyperlinks in this Article:
mailto:tara.parker-pope@wsj.com