

## Birth control patch linked to higher fatality rate

**Report: Device has three times greater risk of stroke, blood clot than pill**

The Associated Press

Updated: 5:33 p.m. ET July 17, 2005

Gingerly, Kathleen Thoren's family gathered around her in the intensive care unit, unable to speak to their beloved sister, daughter, wife, or even stroke her hands. The slightest stimulation might create a fatal amount of pressure on the 25-year-old woman's swollen brain, warned the doctors.

"We were horrified, but we tried to just quietly be with her," said her sister Erika Klein. "In the end, it didn't help."

The mother of three died last fall, just after Thanksgiving, after days of agonizing headaches that the coroner's report said were brought on by hormones released into her system by Ortho Evra, a birth control patch she had started using a few weeks earlier.

She was among about a dozen women, most in their late teens and early 20s, who died last year from blood clots believed to be related to the birth control patch. Dozens more survived strokes and other clot-related problems, according to federal drug safety reports obtained by The Associated Press under a Freedom of Information Act request.

Several lawsuits have already been filed by families of women who died or suffered blood clots while using the patch, and lawyers said more are planned.

### **Risk three times higher**

Though the Food and Drug Administration and patch-maker Ortho McNeil saw warning signs of possible problems with the patch well before it reached the market, both maintain that the patch is as safe as the pill.

However, the reports obtained by the AP appear to indicate that in 2004 — when 800,000 women were on the patch — the risk of dying or suffering a survivable blood clot while using the device was about three times higher than while using birth control pills.

The women who died were young and apparently at low risk for clots — women like Zakiya Kennedy, an 18-year-old Manhattan fashion student who collapsed and died in a New York subway station last April. Or Sasha Webber, a 25-year-old mother of two from Baychester, N.Y., who died of a heart attack after six weeks on the patch last March.

Some doctors, reviewing the Food and Drug Administration reports at the request of The AP, were alarmed. "I was shocked," said Dr. Alan DeCherney, editor-in-chief of Fertility and Sterility and a UCLA professor of obstetrics and gynecology.

But other doctors said they would have expected some deaths and no investigation is warranted. They point to more than 4 million women who have safely used the patch and note that the FDA reports are called in voluntarily, rather than gathered scientifically.

"It doesn't jump out at me to say, 'Let's look at this any further,'" agreed Dr. Steven J. Sondheimer, professor of obstetrics and gynecology at the University of Pennsylvania. "I don't feel that these need to be looked at in any detail."

### **No cause for alarm?**

Ortho McNeil, a subsidiary of Johnson & Johnson, says none of the deaths can be directly attributed to the patch.

"Although we are investigating each and every one of the reports that we get, we have not drawn any causal relationships to the medication," said Dr. Katherine LaGuardia, Ortho McNeil's director of women's health care.

DKL

Not one? "Right," she said. "It's difficult to reach a definitive answer, and privacy laws prevent us from investigating as thoroughly as we wish."

Blood clots are an accepted risk from hormonal birth control because estrogen promotes blood coagulation.

But how many clots are too many?

The AP found that before the patch was approved, the FDA had already noticed nonfatal blood clots from the patch were three times that of the pill. The AP then examined what has actually happened since the patch came on the market and found that deaths also appear to be at least three times as high.

If you are a woman taking the pill who doesn't smoke and is under 35, the chance that you are going to have a blood clot that doesn't kill you is between 1 and 3 in 10,000. Your risk of dying from a blood clot while using the pill is about 1 in 200,000.

By contrast, with the patch, the rate of nonfatal blood clots was about 12 out of 10,000 users during the clinical trials, while the rate of deaths appears to be 3 out of 200,000.

Clots usually form in the legs, and become serious problems if they travel to a woman's heart, lungs or brain.

### **Early warning signs**

In 2000, doctors at the FDA reviewing clinical trials of the wafer-thin, plastic patch warned that blood clots could be a problem if it was approved.

In those trials, two of the 3,300 women using the patch were treated for blood clots that traveled to their lungs. Ortho McNeil says one of those women shouldn't be counted because she had undergone surgery. But an FDA reviewer, using capital letters and underscoring his comments, took issue with Ortho McNeil.

"THE REVIEWER DOES NOT AGREE WITH THE SPONSOR'S ABOVE CONCLUSIONS. The two cases of pulmonary embolus, a serious and potentially fatal condition, must be counted as two cases ...," said the report. "The incidence rates quoted by the sponsor may be misleading."

The reviewer said "the label should clearly reflect this reviewer's safety concern about a potential increased risk." It would be important to study users after the patch came on the market for clot problems, he wrote.

But when the patch was approved in the U.S. in 2001, there were no requirements for follow-up studies beyond routine FDA reviews of reports called in by consumers, doctors and manufacturers.

The label's safety warning says two different and seemingly contradictory things: First, it says the patch is expected to be associated with similar risks as the pill. Then, it says it is unknown if the risk of blood clots from the patch is different from the pill.

The AP reviewed what has happened since the patch came on the market in 2002.

### **Hormones enter bloodstream directly**

The FDA responded to a FOIA request by providing the AP with a database that contained about 16,000 different reports of adverse reactions associated with the patch.

These ranged from mild rashes to deaths, and there were many duplicate reports. Within this collection of reports, the AP found 23 different deaths associated with the patch. The primary cause of death in those reports isn't always clear — some mention suicide, others abortion. Doctors who reviewed the 23 cases found about 17 that appeared to be clot-related, including 12 from last year.

"That number of deaths certainly sounds suspicious," said Dr. Pamela Berens, associate professor of obstetrics and gynecology at the University of Texas Medical School at Houston. "There may be something about the way the drug is metabolized that could increase the risk for clots."

Although the estrogen levels are similar in the patch and the pill, the hormones in a pill must be processed through the intestinal tract before they enter the blood stream. Hormones in the patch, on the other hand, go

DKL

directly into the bloodstream.

Dr. Sidney Wolfe, director of Public Citizen's Health Research Group, a consumer advocacy organization founded by Ralph Nader, said that the deaths and high rate of clots are "worrisome" and should be investigated.

"These days, more often than not the problems with a drug show up after they're approved," he said.

But Dr. Daniel Shames, the FDA's director of the Division of Reproductive and Urological Drug Products, who approved the agency's medical review, said he has reviewed cases of women who died using the patch and saw no cause for alarm.

"We think the death rate here is of concern, but it's not different than what we expect," he said. "As of right now we still believe there's nothing that would precipitate our doing anything additional to follow up on these reports."

And other doctors who prescribe the patch warned that women should not overreact to news of deaths. It is more risky to remove the patch and become pregnant, several pointed out.

### **'You can use a patch safely'**

Dr. Philip Darney, a professor of obstetrics and gynecology at the University of California, San Francisco, and a leading contraceptive researcher, cautioned that the FDA's adverse event reports tend to be inflated for newer products like the patch.

Patients and doctors are more likely to contact the FDA when they have a bad reaction to a new drug than for something that has been on the market for a long time, he said. In addition, women using the patch are likely to either be new to hormonal birth control or have reacted poorly to the pill and are looking for a change. The result is that the pool of women using the patch are at higher risk than birth control users at large.

He tells patients, "If you can use a pill safely, you can use a patch safely, and we're going to know a lot more later as more women use patches," he said.

Ortho McNeil recommended that the AP speak to two doctors, Dr. Hilda Hutcherson, co-director of the NY Center for Women's Sexual Health and a professor at Columbia University Medical Center, and Dr. Vanessa Cullins, vice president of medical affairs at Planned Parenthood Federation of America. Both doctors have served in the past as paid advisers to Ortho McNeil.

Hutcherson said the risks of blood clots from hormones are well known, and that "what has happened with the patch is consistent."

Cullins said she did her own comparison of data for the pill and patch and found the patch is safer than expected.

"My research was to determine whether or not the expected number of deaths from the pill was lower than what was seen with the number of deaths reported with Ortho Evra. I found the opposite," said Cullins, who has done research, consulted for and been a speaker for Ortho McNeil and other drug companies.

Cullins said she reviewed the deaths looking at "women years" rather than current users. Women years is a measure that takes into account that different people use a particular contraceptive for different periods of time. For example, if three women each used a patch for four months, that would count as one woman year rather than three current users.

Cullins reviewed patch users from 2002, when the patch came on the market, until late 2003. For that period, Cullins said she would have expected 22 deaths and found only 6.

The AP reviewed the deaths looking at both women years and current users, but used more recent data, focusing on 2004 when the patch had been much more widely adopted.

*© 2005 The Associated Press. All rights reserved. This material may not be published, broadcast, rewritten or redistributed.*

DKL

URL: <http://www.msnbc.msn.com/id/8565177/>