Tough restrictions have not stopped Accutane pregnancies. Doctors see ways to do better

August 13 2019, by Marie Mccullough

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It has been 13 years since the U.S. Food and Drug Administration took a bold step to prevent birth defects caused by the only drug that can cure severe acne.

Women were still getting pregnant while taking isotretinoin, branded as Accutane, despite two decades of restrictions and precautions. So in 2006, the FDA imposed iPLEDGE, a stringent registry program—one that dermatologists immediately called a burdensome, confusing mess.

Pledge brochures say the registry data is used to assess the effectiveness of the program and improve it.

But the FDA has not publicly shared that data or said whether it thinks iPledge has succeeded.

Now, a new study concludes it has not.

By mining the FDA's public database of reports of "adverse events" from drugs, researchers found 6,740 pregnancies among women on isotretinoin from 1997 to 2017.

iPLEDGE did not lower the rate of fetal exposure more than the previous pregnancy-prevention program. And while the absolute number of pregnancies per year has fallen since the peak of 768 in 2006, it plateaued in 2011. Every year since then, about 200 to 300 isotretinoin users have gotten pregnant, the study found.

"iPLEDGE may not be deterring pregnancies," said University of Pennsylvania dermatology research fellow John Barbieri, a co-author of the study published last month in JAMA Dermatology. "The flip side is we're seeing that iPLEDGE may be having the unintended consequence of discouraging use by people who need the drug."

Meagan Fox, 26, a suburban Denver esthetician who moderates the Facebook group Girls Helping Girls with Accutane, was not surprised by the findings.

Last year, while taking isotretinoin for five months to get rid of her cystic acne, Fox committed—as iPledge requires—to using two forms of birth control. Even though she already had a contraceptive implant that is 99% effective, she and her longtime boyfriend added condoms.

But some women are exempt from that requirement. All they have to do is promise not to have sex.

"To make iPledge more effective, first, eliminate the option to be abstinent," Fox said. "It just doesn't work."

Some doctors close that iPLEDGE loophole.

"I don't take abstinence as a valid form of contraception," said Nazanin Saedi, a dermatologist and laser surgeon at Thomas Jefferson University Hospital. "I tell them, 'The birth defects can be horrific. I would sleep better at night knowing you are on some form of contraception.'"

Asked for comment, the FDA emailed: "Information in the pregnancy registry is confidential ... The iPLEDGE program is robust when implemented as designed."

A Breakthrough Therapy

The 1982 debut of Accutane, a vitamin A derivative, was a watershed in dermatology. Suddenly, a common, stubborn condition that was both physically and emotionally scarring could be cured, or close to it, usually with tolerable side effects like temporary chapped lips and peeling skin. (Accutane developer Hoffmann-la Roche sold the product to 13 million people before quitting in 2009, ceding the market to generic versions. Still, the well-known name persists.)

Meagan Fox's acne all but disappeared during five months on

isotretinoin.

Isotretinoin triggered depression in some users, but that could be monitored during the five or six months of treatment.

Accidental pregnancies were a thornier issue. Most of them ended in abortion or miscarriage, but about 1 in 4 babies who were born had brain, heart, or facial deformities, research showed. Even brief exposure to the drug could be devastating.

Given the fallibility of humans—and of the most commonly used birth control methods—the manufacturer, doctors and regulators alike recognized that completely eliminating the risk would be impossible.

But it was clear that many doctors and female patients were not complying with safeguards such as pregnancy tests and contraceptive counseling.

A Roche survey of 300,000 women treated in the 1990s found 23% never signed consent forms, 25% had no initial pregnancy tests, and a third who had tests started the drug without results. A government study of 14 women who got pregnant found eight had sex without birth control and two got the drug from friends. One of them didn't even have acne; she just popped a few capsules before her period to prevent oily skin.

iPledge aimed to ensure women understood the dangers, and clamp down on improper access.

Like the preceding pregnancy-prevention program, iPledge limits patients to a 30-day supply of isotretinoin at a time. It requires two negative lab-based pregnancy tests before treatment starts, monthly pregnancy tests and doctor's office visits, and two forms of birth control or abstinence.

But iPledge, developed by regulators and manufacturers, goes further. It has a deadline-driven, computer-based registry system that requires careful coordination between doctors, female patients and pharmacists. Each month, the doctor's office and the patient must document compliance, online or by phone. If there's a misstep, the patient gets "locked out" and either has to skip a month of treatment, or scramble to satisfy the system by calling the toll-free number.

The prescription, for example, has to be picked up within seven days of the negative pregnancy test or the pharmacist can't dispense it. "If your 7-day prescription window expires before you obtain your prescription," says the female patient handbook, "you must repeat the program requirements."

"Happens all the time," Saedi at Jefferson said. "I understand why it's so tightly regulated, but now that we're 13 years out, there should be a way to streamline and improve it."

Women who can't get pregnant and men have more lenient provisos, but still must register and have monthly doctor visits.

Barbieri, at Penn, said the monthly appointments often conflict with jobs, school, summer camp, travel—in a word, life.

A study of 418 patients found that iPledge-related logistical hassles led 30% of white patients and 44% of non-white patients to delay treatment, interrupt it, or quit early. The study's senior author, Harvard Medical School dermatologist Arash Mostaghimi, was part of the new research on pregnancies.

Try Giving Incentives

Although the FDA says iPLEDGE data is confidential, numbers from

four years—2006, 2008, 2009, and 2010—were presented publicly at a 2011 advisory committee meeting.

The new study used that data, plus the adverse event reports, to calculate rates of pregnancies, abortions, and fetal defects for those four years.

The risk of pregnancy ranged from 0.65% in 2006 (768 pregnancies among 117,784 women) to 0.33% in 2009 (388 pregnancies among 115,925 women). That was not lower than the 0.29% rate calculated by a study of the preceding pregnancy-prevention program, called SMART (System to Manage Accutane Related Teratogenicity).

The new study found the risk of fetal defects was far lower than the 18% to 28% estimated by earlier research, but that could have been because of incomplete reporting to the FDA's adverse event database. A total of 210 fetal defects were reported from 1997 to 2017.

"The numbers are still unacceptable," said Rahul Gupta, chief medical officer of the March of Dimes, which pushed for iPledge. "The study is a good time to go back and reevaluate the program and determine what is the most prudent approach for these women while they're on this drug."

Toward that end, the American Academy of Dermatology Association recently formed a task force that plans to make recommendations to the FDA later this year. One member, Laura K. Ferris of the University of Pittsburgh Medical Center, has long advocated counseling and enticements to get women to use almost-perfect birth control methods—namely, the IUD or the contraceptive implant. (Under the Affordable Care Act, all methods must be covered by insurance with no out-of-pocket costs.)

"Give them incentives," Ferris said. "We could tell them, 'If you use one

of these forms, you don't have to use condoms. One form is enough.' And we could reduce the frequency of pregnancy tests—maybe every other month."

Barbieri and his co-authors suggest giving emergency contraception, the so-called morning-after pill, with isotretinoin prescriptions, and doing clinical studies to see what strategies work best.

"I think we have opportunities to take advantage of what we've learned to be more effective in reducing pregnancies," Barbieri said.