

ENDOCRINOLOGY

Mice Prompt Look at Cholesterol's Role in Female Fertility

It's easy to forget that cholesterol isn't simply a villain. The white, waxy substance is famously intertwined with heart disease, but cholesterol lives all over the body, building cell membranes and hormones. A small group of researchers is now wondering whether cholesterol also helps maintain fertility—and whether cholesterol abnormalities impair a woman's ability to get and stay pregnant. There's even speculation that a cholesterol-lowering drug, which is no longer on the market, could treat a subset of women who are battling infertility.

The complicated story starts more than 15 years ago, when Monty Krieger, a molecular geneticist at the Massachusetts Institute of Technology in Cambridge, discovered a cell membrane protein, scavenger receptor class B, type I (SR-BI). The receptor binds to high-density lipoproteins (HDL) and sucks out their lipids, clearing them from the blood. Unlike cholesterol-laden low-density lipoproteins (LDL), which can harm the arteries, HDL is generally considered the “good” cholesterol. Researchers theorize that that's because the particles remove cholesterol from arteries, and companies are even seeking drugs to raise HDL levels in the blood in order to prevent heart disease.

Krieger engineered mice to lack SR-BI, and as expected, they had high HDL cholesterol levels because the receptor wasn't available to facilitate their clearance. But the

mice had two surprising features: They had severe heart disease despite high HDLs, and the female rodents, but not the males, were also infertile.

Krieger set to work trying to solve both puzzles. The infertility puzzle also soon

“Could women at an infertility clinic have a similar problem?”

—ANNABELLE RODRIGUEZ,
JOHNS HOPKINS UNIVERSITY

intrigued Annabelle Rodriguez, an endocrinologist at Johns Hopkins University in Baltimore, Maryland, who cares for adults with cholesterol disorders. “We said, ‘Could women at an infertility clinic have a similar problem?’” she recalls. The question was particularly compelling as Krieger had found that he was able to cure the infertility in the female mice with a cholesterol drug called probucol that lowers both LDL and HDL levels.

Admittedly, probucol is not the most promising drug to give to women trying to get pregnant: It was removed from the market in the 1980s because it causes a potentially fatal heart condition. Still, the idea that a simple drug might cure some infertility was so appealing that Rodriguez forged

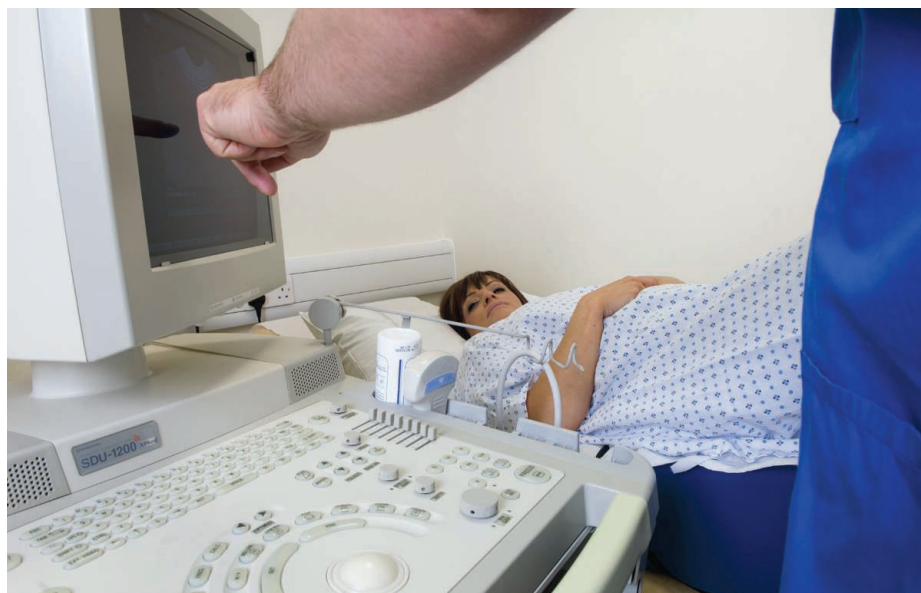
ahead to see if Krieger's story held up in humans. In 2009, Rodriguez found that people whose cells have fewer SR-BI proteins than normal tended to have higher HDL levels, suggesting that its function was similar in mice and humans. And last year, she

reported that the same receptor deficiency was associated with lower-than-average progesterone levels.

More recently, Rodriguez has turned to women coming to the Johns Hopkins in vitro fertilization (IVF) clinic because of fertility issues. There, she found that about 15% of the women tested had one or two copies of SR-BI gene variants previously associated with low production of the protein. More-

over, those women also had, on average, lower progesterone levels than women without the variants, according to Rodriguez's measurements of the hormone in the follicular fluid that surrounds a woman's egg. Nine women with one of the SR-BI variants were also unable to sustain a pregnancy after receiving their IVF embryo. In contrast, among those without that variant who had an embryo transfer, 207 women in all, about 30%, were able to get pregnant.

Rodriguez believes that the IVF clinic findings, published in *Human Reproduction* at the end of April, echo what Krieger saw in mice. Why would a dearth of production of SR-BI cause infertility? No one's really sure, but there are theories. An early one revolved around steroid hormones, like estrogen and progesterone, to which cholesterol is a precursor. Unlike some hormones, such as insulin, which the body stores and releases when needed, steroid hormones are made from scratch on demand, and cholesterol is the key ingredient. But Krieger found that in his mice lacking SR-BI, HDL cholesterol hangs around in the blood because it moves more slowly to other tissues. This could impair ovarian production of hormones such as estrogen and progesterone, which help control egg production or ready the lining of the uterus for implantation of a new embryo. Indeed, a study by a group in Montreal, published in April 2010 in the *Journal of Lipid Research*, found that mice lacking SR-BI had blood levels of progesterone about 50%



New fertility player. Cholesterol is increasingly being eyed for a role in helping women become or stay pregnant.

below normal. That's nearly identical to what Rodriguez observed in the follicular fluid of the women with the gene variants tied to poor SR-BI production.

Is the problem in mice and people too little progesterone due to too much HDL cholesterol in the blood? Krieger isn't convinced by the theory, noting that his mice had a normal menstrual cycle—something that's not possible without passable hormone levels. He has, however, found defects in the mouse eggs as they are ovulated and hypothesizes now that the problem, at least in mice, has something to do with cholesterol's impact on oocyte maturation. Rodriguez says she still favors the idea that progesterone is a problem for the women in her study, but she's stymied by limited information. In particular, she doesn't know the HDL levels of the women with SR-BI variants, because fertility clinics don't normally measure cholesterol, nor does she know if they had a normal menstrual cycle.

Muddling the picture further is a large family in southern Holland, many members of which were known to have high HDL levels. Those members have one mutated copy of the SR-BI gene, Jan Albert Kuivenhoven of the Academic Medical Center in Amsterdam and colleagues reported in January in *The New England Journal of Medicine*. Yet several of the affected women with a high HDL level nevertheless had children. "Fertility problems were certainly not in this family," Kuivenhoven says. Despite that, the lipidologist doesn't discount Rodriguez's work. The numbers in this family "are too small" to say anything definitive about fertility, he says.

Rodriguez says she has just submitted a grant application to the U.S. National Institutes of Health to study how SR-BI variants affect the menstrual cycle in women of child-bearing age, not just those undergoing IVF. She is also working on an investigational new drug application to test probucol in infertile women with SR-BI deficiency.

"We are just in the infancy of trying to understand" cholesterol's effects on fertility, says Victor Fujimoto, a reproductive endocrinologist at the University of California, San Francisco, who has found that a plentiful supply of HDL cholesterol helps keep IVF embryos in good health in the lab before they're transferred to women. Fujimoto acknowledges that exactly how this happens remains unclear, but whatever the answer, the broad-brush strokes are forming a clearer picture: Cholesterol seems to matter when it comes to fertility, at least in women.

—JENNIFER COUZIN-FRANKEL

Testing, testing. China is stepping up HIV testing, but a positive result can have serious social consequences.



CHINA

Stigma of HIV Imperils Hard-Won Strides in Saving Lives

BEIJING—Encouraged by last month's news that AIDS mortality has plummeted in China, authorities here are embarking on a new 5-year plan for tackling the epidemic that includes ambitious targets for case detection and access to treatment. But further gains are jeopardized, critics warn, by rampant discrimination against HIV-infected individuals and the entrenched stigma of homosexuality in China.

"HIV/AIDS prevention is not just a clinical matter," says Joseph Lau, a public health expert at Chinese University of Hong Kong. "There are serious social and culture barriers to overcome to ultimately win the battle against the disease."

By the end of 2010, China had recorded 379,348 cases of HIV infection, including 138,288 people who had developed AIDS, and 72,616 deaths, according to Wu Zunyou, director of the National Center for AIDS/STD Control and Prevention of the Chinese Center for Disease Control and Prevention (CDC) here. After years of virtually ignoring the epidemic, China introduced antiretroviral therapy to treat HIV-infected people in 2002. That move made a huge difference: In *The Lancet Infectious Diseases* on 19 May, Chinese CDC researchers reported that AIDS mortality in China declined 64% between 2002 and 2009. Mortality rose slightly last year.

But for thousands of Chinese, interventions are coming too late, or not at all. CDC

estimates that there are 740,000 HIV-infected people—twice the reported number. Many AIDS patients in China are gravely ill by the time they are first tested for HIV, says Hao Yang, deputy director of disease prevention and control at China's health ministry. In 2010, a quarter of those who tested positive had already developed AIDS, and nearly half of the partners of HIV-infected people were infected; among fatalities, 82.4% died before getting treated. "Early detection remains the biggest challenge," Wu says.

In the new 5-year action plan, China aims to reduce new infections by 25% and the fatality rate by 30% by 2015, Wu says. To achieve those targets, the government will expand detection programs, aiming to diagnose 75,000 cases this year, up 16.6% from 2010, and put more than 40,000 more people on treatment; by the end of last year, 108,800 people were on antiretroviral drugs. Hospitals in regions with high infection rates intend to impose mandatory HIV testing for patients and for high-risk populations, including sex workers, injecting drug users, and men who have sex with men (MSM).

Many experts warn that the strategy is likely to backfire. "Mandatory HIV testing may pose threats to individuals' rights," says Zhang Konglai, an epidemiologist here at the Institute of Basic Medical Sciences of the Chinese Academy of Medical Sciences (CAMS). "There are reasons why people don't want to