Gene variation linked to infertility in women, study finds

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A variation in a gene involved in regulating cholesterol in the bloodstream also appears to affect progesterone production in women, making it a likely culprit in a substantial number of cases of their infertility, a new study from Johns Hopkins researchers suggests.

The Hopkins group has also developed a simple blood test for this variation of the scavenger receptor class B type 1 gene (SCARB1) but emphasized there is no approved therapy yet to address the problem in infertile women.

Following up studies in female mice that first linked a deficiency in these receptors for HDL — the so-called "good" or "healthy" cholesterol — and infertility, researchers report finding the same link in studies of women with a history of infertility. If the new study's findings hold up on further investigation, the John Hopkins team says they not only will offer clues into a genetic cause of some infertility, but could also lead to a treatment already shown to work in mice.

"Infertility is fairly common and a lot of the reasons for it are still unknown," warns endocrinologist Annabelle Rodriguez, M.D., an associate professor of medicine at the Johns Hopkins University School of Medicine and the leader of the study published online in the journal *Human Reproduction*. "Right now, the benefit of this research is in knowing that there might be a genetic reason for why some women have difficulty getting pregnant. In the future, we hope this knowledge can be translated into a cure for this type of infertility."

Between November 2007 and March 2010, Rodriguez and her colleagues analyzed ovarian cells and fluid collected from 274 women unable to become pregnant for various reasons and undergoing in vitro fertilization (IVF). Some 207 of them went on to have their eggs collected, fertilized in a test tube and implanted in their wombs.

The scientists then measured whether there was evidence of a gestational sac or a fetal heartbeat 42 days after embryo transfer. None of the nine women in the group found to have the mutated SCARB1 had such evidence, meaning none were pregnant.

Rodriguez says she believes the genetic variation could be present in 8 to 13 percent of the population.

The researchers also showed that the nine women with the altered gene had low levels of progesterone, a hormone critical to sustaining pregnancy in its earliest stages, despite being supplemented with progesterone as part of the IVF process.

Rodriguez, who is also director of the Johns Hopkins Diabetes and Cholesterol Metabolism Center, based her work on research with mice genetically engineered without the receptor for good cholesterol. Without the receptor, the mice had abnormally high levels of HDL in the blood since their bodies were unable to uptake the cholesterol. They were also at increased risk for heart disease, and the female mice were infertile.

The Massachusetts Institute of Technology researchers who studied the genetically engineered mice also found a treatment for their infertility in a cholesterol medication developed decades ago. Called probucol, it lowered levels of cholesterol circulating in the blood and restored the rodents' fertility. The drug is no longer approved for use in the United States, partly because of concerns that it unsafely lowers HDL, but that

very "side effect" seemed a good fit for mice with missing HDL receptors. It is available in Japan for use in some conditions.

"I'm an optimist that this drug or one like it could also restore fertility in women," Rodriguez says. "Everything else that was found in mice so far has borne out in humans."

In the very near future, Rodriguez hopes to conduct a clinical trial to see if probucol can help infertile women with the gene variation get pregnant. She is also planning to collect data on HDL levels in infertile women with the genetic variation to see if that would prove to be an early clue to a genetic cause of their infertility.

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