

## Statins may prevent miscarriages

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Hospital for Special Surgery researchers have found that statins may be able to prevent miscarriages in women who are suffering from pregnancy complications caused by antiphospholipid syndrome (APS), according to a study in mice. In this autoimmune syndrome, the body produces antibodies directed at phospholipids, the main components of cell membranes. This news comes from a study published in the October issue of the *Journal of Clinical Investigation* that is currently online in advance of print.

In low risk pregnancies, APS is associated with a nine-fold increase in miscarriage. In high-risk pregnancies (women who have had at least three prior losses), APS is associated with a 90 percent risk of miscarriage.

"Statins may work as a treatment for women with APS-induced pregnancy complications," said Guillermina Girardi, Ph.D., associate scientist at Hospital for Special Surgery in New York, who is lead author of the study. "They are drugs that have been shown to be very safe. There are a lot of women who continue to take statins through pregnancy and the drugs have not been shown to produce birth defects." Statins do not increase the risk of bleeding like anticoagulants, the current treatment for patients with APS.

In previous studies, Dr. Girardi and colleagues showed that antiphospholipid (aPL) antibodies in female mice caused inflammation that injured the placentas and induced abortions. These antibodies activate a protein, C5a, that activates another protein, tissue factor, that

is expressed on the surface of certain white blood cells called neutrophils. This spurs the neutrophils into action, they attack the placenta, and the fetus dies. While investigators had unveiled this basic chain of events, they didn't know any further details about the mechanism.

To find out, Dr. Girardi and colleagues examined the white blood cells from mice that had APS and discovered that these cells expressed certain receptors called PAR2 (protease-activated receptor 2). Stimulating this receptor led to the activation of white blood cells that attacked the placenta and hurt the fetus. Using an antibody that blocks tissue factor interaction with PAR-2, they inhibited white blood cell activation.

In another experiment, investigators tested a possible treatment. Previous studies had shown that statins, commonly used to regulate cholesterol levels, could downregulate tissue factor (diminish the number of molecules expressed on the surface of the cell). Dr. Girardi and colleagues found that statins not only downregulate tissue factor, but they also downregulate PAR-2 on white blood cells, making the cells less sensitive. So, the researchers injected statins into mice with APS and found that these drugs could prevent white blood cell activation and protect pregnancies.

Women are advised to discontinue most medications, including statins, during pregnancy, but Dr. Girardi says that no fetal defects have been reported in women who have continued to use statins while pregnant. The researchers say that careful studies should be conducted to confirm the safety of statins in pregnancy in humans. "Women that are antiphospholipid antibody positive and have a history of previous miscarriages are a good group to perform a clinical trial," Dr. Girardi said.

On average, 50 percent to 70 percent of all conceptions fail. There is an association between circulating aPL and pregnancy loss, and between 3 percent and 7 percent of pregnant women have these antibodies.

This study could also have implications for other conditions. "The study reveals a relationship between tissue factor and PAR2 in inflammation that could have implications for understanding chronic inflammatory conditions such as rheumatoid arthritis," said Dr. Girardi. Tissue factor expression on cells that line the circulatory system and certain immune cells is a characteristic feature of acute and chronic inflammation in conditions such as sepsis, atherosclerosis, Crohn's disease, and lupus. Finding a way to manipulate tissue factor and PAR2 could lead to treatments for these diseases.

Source: Hospital for Special Surgery

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