Researchers pinpoint possible new cause for unexplained miscarriages

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Researchers at St. Michael's Hospital have identified a potential new cause for unexplained miscarriages in mice.

They also identified two possible treatments to prevent these miscarriages and their work has broader implications for the development of new drugs to treat heart attacks and strokes.

The researchers, led by Dr. Heyu Ni, found that the same kind of blood-clotting in coronary arteries or blood vessels in the brain that causes heart attacks and strokes also happens in the placenta. The massive clotting can destroy the placenta, block blood flow to the fetus and cause miscarriages.

This condition is known as fetal and neonatal immune thrombocytopenia (FNIT), a bleeding disorder in which mothers generate antibodies that attack and destroy platelets in their fetuses and newborns. Platelets are the small cells in the blood that play a key role in clotting. In severe cases, FNIT may lead to bleeding in the brains of the fetuses and newborns and cause neurological impairment or even death.

The condition affects between one in 800 and one in 1,500 live births and is more commonly reported among Caucasians.

Maternal antibodies to one specific platelet antigen, HPA-1 (human platelet antigen) cause 75-95 per cent of FNIT cases. Antigens are the proteins that antibodies attack because they think they are a foreign substance such as bacteria or a virus.

Dr. Ni and his team discovered a novel mechanism that might partially explain this problem. They found that another antigen, HPA-2, causes a type of FNIT never described before that can lead to miscarriages in more than 83 per cent of mice. There have been only six to eight reported live births in the world of humans with FNIT caused by HPA-2. The new research suggests the reason these cases appear to be so rare is that most of the affected fetuses died through miscarriages, before doctors examined them.

Dr. Conglei Li and other researchers in Dr. Ni's laboratory found that sometimes these antibodies not only destroy platelets, but activate them and cause massive clotting in the placentas.

Dr. Ni, an immunologist, is also a scientist with Canadian Blood Services (CBS), one of the funders of this research. His findings appear in the November issue of the prestigious *Journal of Clinical Investigation*.

Dr. Ni's group demonstrated that, in mice, these miscarriages can be prevented using at least two therapies. One is the transfusion of IgG (IVIG), a CBS product made from plasma from donated blood, which has been widely used to treat several autoimmune diseases. The other is the transfusion of an antibody known as anti-FcRn, which blocks the attacking maternal antibodies from crossing the placenta. This second method was developed by Dr. Ni's group.

"Fifty per cent of pregnancies do not end in a live birth. Our findings may help explain why some women are having miscarriages," said Dr. Ni. "Furthermore, our treatments could be the answer to carrying a healthy child to term."

The observations by Dr. Ni's team of platelet activation and enhancement of clotting may be important in the development of safer anti-thrombotic drugs. These drugs are under development by several companies.

Dr. Ni's group is now collaborating with clinicians to address how relevant these discoveries in mice are in humans.

Provided by St. Michael's Hospital