Study shows how fetal infections may cause adult heart disease

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A caregiver's hand cradles the feet of a preterm infant in the University of Washington Medical Center Neonatal Intensive Care Unit. Credit: UW Medicine

Recent studies have shown that infants born prematurely have a higher risk of developing heart disease later in life. Now, a study led by

researchers at the University of Washington School of Medicine in Seattle shows that, in preterm animal models, inflammation due to infection can disrupt the activity of genes that are crucial for normal development of the heart

"This study connects the dots between preterm birth and heart disease in adult life by defining the gene networks disrupted by infection and inflammation that program normal heart development," said lead author Dr. Kristina Adams Waldorf, a professor of obstetrics and gynecology at the University of Washington School of Medicine who specializes in maternal and fetal infections.

"When I was in training," she said, "we talked to women in preterm labor about the risk to their infants of lung and brain injury. We now know that long-term health risks of a preterm birth extend beyond the developing lungs and brain to involve vision, hearing, kidney and even heart function."

The study appears in the Jan. 23 online edition of the *American Journal of Obstetrics & Gynecology*.

Dr. Lakshmi Rajagopal, an associate professor of pediatrics at the University of Washington School of Medicine and expert on newborn infectious diseases at Seattle Children's Research Institute and UW Medicine, and Dr. Timothy Mitchell, an obstetrician specializing in high-risk pregnancies and a former UW Medicine fellow in maternal and fetal medicine, led the study with Adams Waldorf.

"This study is the first to show that the gene program for heart development in preterm babies is interrupted in preterm babies exposed to fetal infection and inflammation, which may lead to incomplete heart development," said Mitchell. "This incomplete development, in turn, may be lead to the higher risk of abnormal heart rhythms and heart

failure seen when preterm babies reach adulthood."

The researchers studied the heart tissue from fetal pigtail macaque monkeys whose mothers' uteruses had been infected with bacteria, namely Group B Streptococcus and Escherichia coli. These often cause infections in human mothers and trigger preterm birth.

The investigators compared gene expression patterns from fetal heart tissues infected with bacteria to normal heart tissues. The animals were chosen because macaques are considered one of the closest animal models to human pregnancy. They also are ideal for the development of vaccines and treatments to protect pregnant women from bacterial infections.

The infections in these experiments were severe, a scenario that is typical of early preterm births, which occur in approximately 2 percent of all U.S. births. Infection triggered a marked inflammatory response in the fetus.

Inflammation was also present in the heart tissues and characterized by elevations in inflammatory proteins, like interleukin-6 and interleukin 8.

A preterm infant receives treatment in the Neonatal Intensive Care Unit at University of Washington Medical Center. Credit: UW Medicine

Many of the genes with altered expression—NPPA, MYH6 and ACE2—have known functions in heart development or are linked to heart disease. For example, the gene NPPA, which encodes Natriuretic peptide A, is essential for the formation and expansion of the walls of the heart.

The researchers also found significant alteration in the expression of gene networks involved in heart and blood vessel formation, including the movement and migration of cells, growth of smooth and cardiac muscle, and the migration of endothelial cells that line the inside of the

heart and blood vessels.

"These findings suggest that many pathways related to fetal heart development may be impacted by inflammation and infection," said Mitchell.

"We are only beginning to understand the health risks that infection and inflammation pose to the developing fetus, particularly in the setting of an early preterm birth," added Rajagopal. "We need a better understanding of how bacteria invade the uterus to cause preterm birth so that we can develop therapies to prevent fetal infections. Ultimately, we must also develop an effective vaccine for Group B Streptococcus to protect pregnant women and their fetuses."

"Future research should investigate whether combining antibiotics to treat the infection and anti-inflammatory drugs can lessen inflammation and damage to the fetal heart," noted Adams Waldorf. "If we can better understand how to prevent infections that cause preterm birth, we can protect fetuses and enhance their long-term health into adulthood."

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