Pregnant women with hepatitis C may pass heartier viral strain to newborns, study suggests

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Infants who get hepatitis C from their mothers during childbirth may inherit a viral strain that replicates more quickly than strains found in non-pregnant hosts, according to a new study published Oct. 27 in *Nature Medicine*. The findings, from a team in The Research Institute at Nationwide Children's Hospital, are the first to describe how a virus that has infected 180 million people worldwide takes advantage of immune changes during pregnancy.

About 1 percent of all pregnant women worldwide have hepatitis C, caused by a highly adaptable virus known as HCV that infects liver cells. In 3 to 5 percent of these pregnancies, the virus is passed to the newborns, accounting for the majority of new childhood HCV infections. Between 15 and 45 percent of people infected with HCV are able to mount an immune response sufficient to eradicate the virus. But in most cases, the virus eludes immunity, leading to a chronic infection that increases the risk of liver failure or liver cancer.

As part of a larger study of HCV in pregnant women and infants, researchers at Nationwide Children's followed two women with hepatitis C over a five-year period. Both women had two children during this time, and researchers were able to track the virus before, during and after pregnancy. Their analysis revealed surprising changes in HCV genomes that not only allowed the virus to thrive, but also ensured that the strain passed on by one of the women during childbirth was

particularly good at replication, says Jonathan R. Honegger, MD, an infectious disease specialist and principal investigator in the Center for Vaccines and Immunity at Nationwide Children's.

"We found that better replicating versions of the virus emerged during pregnancy, and these 'fit' viruses were passed to the babies." Dr. Honegger says. "The findings actually provide unique insight into the impact of pregnancy on the mothers' control of viral infections, and also a striking illustration of this virus' ability to adapt to changing environmental pressures."

HCV persists in the general population, in part, because the virus outwits the immune system with mutations that can render it undetectable to CD8+ T-cells, important weapons in the body's antiviral immune arsenal. Although these viral variations—called immune escape mutations—protect the virus from attack by T-cells, they sometimes slow the virus replication machinery.

During pregnancy, T-cells are restrained to prevent the body from attacking the fetus as foreign tissue. Viral levels of HCV have also been known to increase during pregnancy, but whether this was related to changes in T-cell function was unknown. Working closely with Chris Walker, director of the Center for Vaccines and Immunity, and colleagues at Emory University and the University of North Carolina, Dr. Honegger found that during pregnancy, certain T-cell escape mutations were lost, resulting in a virus that could replicate far more quickly.

"This surprised us because the virus' immune escape mutations are usually stable in a patient," Dr. Honegger says. "The loss of these immune escape mutations from HCV during pregnancy provided strong evidence that the immune changes of pregnancy, intended to protect the fetus, significantly impaired the ability of CD8+ T-cells to exert pressure

on the virus."

Loss of the escape mutations also meant that the babies got a version of the virus that was optimized for viral replication, Dr. Honegger adds. In the children they studied, the virus persisted and did not mutate in a way to suggest that it was under significant attack by their CD8+ T-cells.

"We don't yet know whether getting the fast-replicating, immune-susceptible version of the virus would be an advantage for the baby or the virus," says Dr. Honegger, who also is an assistant professor of pediatrics at The Ohio State University. "We suspect that if the baby doesn't mount a swift and strong immune response, then fast viral replication may increase the risk of persistent infection in the baby."

On the other hand, viral loads in the mothers dropped more than 1,000 fold by 12 weeks after delivery and viral genetic analysis showed that immune escape mutations had returned. "We interpreted this to mean that T-cell activity against hepatitis C in the liver increased sharply after delivery," Dr. Honegger says.

Researchers now are following a larger group of pregnant women with HCV, hoping to learn more about how viral mutations affect the way the body controls hepatitis C in pregnant women and infants.

"We believe that better understanding of the natural history of the infection in these patients will be critical for designing rational strategies to treat or prevent HCV in these populations."

More information: Honegger JR, Kim S, Price AA, Kohout JA, McKnight KL, Prasad MR, Lemon SM, Grakoui A, Walker CM. Loss of Immune Escape Mutations During Persistent HCV Infection in Pregnancy Enhances Replication of Vertically Transmitted Viruses. *Nature Medicine*. 2013 Oct 27. DOI: 10.1038/nm.3351 [Epub ahead of

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