Dampened immunity during pregnancy promotes evolution of more virulent flu

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During pregnancy, a mother's immune system is suppressed to protect the fetus, which is perceived as a foreign body because it is genetically different. A study in mice found that suppressed immunity during pregnancy creates a window of opportunity for the H1N1 influenza virus to infect the mother and to rapidly, within a few days, mutate into a more virulent strain. The findings appear in *Cell Host & Microbe* on March 8. More research is required to determine if similar viral mutations occur in pregnant humans.

"The first line of defense of the immune system, the innate immune response, is not acting quickly enough to clear the virus," says co-lead author Gülsah Gabriel, a virologist at the Heinrich Pette Institute, Leibniz Institute for Experimental Virology in Hamburg, Germany. "The virus takes advantage of this permissive environment and mutates very fast. This is what influenza viruses do best. The new variants are responsible for increased virulence."

For the last century, study after study has shown that pregnant women suffer more severely from influenza than non-pregnant women. A 2010 World Health Organization analysis of the 2009 H1N1 influenza pandemic found that pregnant women were 7 times more likely to be hospitalized and twice as likely to die from H1N1 infection than non-pregnant women.

In response, Gabriel and co-lead author Petra Clara Arck, a reproductive immunologist at the University Medical Center in Hamburg, joined

forces to understand the biology behind these observations. Previous studies of influenza evaluated mice that were pregnant with genetically identical fetuses, called syngenic pregnancies. These pregnancies do not mimic natural human pregnancies, in which babies are the product of the combined genes of a mother and father.

So, using mice, Gabriel and Arck also studied allogenic pregnancies, in which the fetuses differ genetically from the mother. In allogenic pregnancies, they found that the immune system is more suppressed than in syngenic pregnancies.

The immune system typically mounts waves of defense against viral infections. Cells in the innate immune system respond immediately by secreting inflammatory factors called cytokines to stop the spread of infection. As the infection progresses, adaptive immune cells called T cells move to the area of infection, where they detect and kill infected cells.

To understand immune suppression in mice with genetically distinct pregnancies, the researchers examined gene expression patterns in immune cells during infection. They found that the genes responsible for releasing cytokines were suppressed, resulting in a weak initial response to infection. In addition, genes responsible for activating and recruiting T cells to an infection were also suppressed. "The entire immune system is damped down to protect the fetus," says Arck.

Influenza appears to take immediate advantage of the mother's vulnerability, according to the study. During the first days of infection, a typical innate immune response will stop the spread. But during pregnancy, the initial response is not strong enough to stop the virus. Rather, surviving viral invaders have time to mutate and produce a range of variants, some of which are more likely to cause a severe infection.

The most frequent mutation the researchers found in influenza in pregnant mice was a variant that further dampens the innate immune response, giving the virus an even better chance to survive and thrive. "In this environment of a dampened innate immune system, the virus has a chance to escape and become more virulent," says Gabriel. "This suggests that during pregnancy, a typical influenza infection could hit very hard."

To determine if pregnant women experience a similar evolution of influenza infection, Gabriel and Arck are planning to look for similar mutations in samples from pregnant women who suffered from influenza. Similar mutations have been seen in other influenza cases in pregnant women, but not in studies large enough to confirm that they are more frequent than other variants.

If a larger study confirms that these variants are seen more commonly in pregnant women, that would further strengthen the importance of influenza vaccinations for pregnant women. "The best bet for pregnant women is to be vaccinated to prevent infection, because influenza viruses are very good at escaping," says Gabriel.

In response to the 2009 H1N1 influenza pandemic, the World Health Organization made pregnant women the number one priority for vaccination, with a goal of vaccinating 75% of this population. The flu shot is safe and protects both the mother and the fetus from infection. According to the CDC, in the US in 2016, about 50% of pregnant women got the flu shot, an improvement over the 20% vaccinated in 2009.

More information: "Pregnancy-related immune adaptation promotes the emergence of highly virulent H1N1 strains in allogenically-pregnant mice," *Cell Host & Microbe*. DOI: 10.1016/j.chom.2017.02.020

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