In vitro study helps explain how Zika virus passes from mother to fetus during pregnancy

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Ozlem Guzeloglu-Kayisli, PhD, USF Health associate professor of obstetrics and gynecology, was the paper's lead author. Credit: Allison Long, USF Health Communications and Marketing

A preclinical study by a University of South Florida Health (USF Health) Morsani College of Medicine research team has discovered a new mechanism for how Zika virus can pass from mothers to their children during pregnancy—a process known as vertical transmission.

The researchers showed, for the first time, that specialized cells lining the uterus (maternal decidual cells) act as reservoirs for trimester-dependent transmission of the virus through the placenta—accounting for both the fetus's greater susceptibility to first-trimester Zika infection and for the more serious congenital defects observed in early versus late pregnancy. They also report that the agent tizoxanide inhibits ZIKA virus in maternal decidual cells grown in the lab, offering promise for preventing perinatal transmission that can cause devastating malformations and brain damage in developing fetuses and infants.

The findings appeared Dec. 1, 2020 in the *Journal of Immunology*.

The study was led by co-principal investigators Ozlem Guzeloglu-Kayisli, Ph.D., a USF Health associate professor of obstetrics and gynecology, and Charles J. Lockwood, MD, USF Health senior vice president, dean of the Morsani College of Medicine, and a professor of obstetrics and gynecology specializing in maternal-fetal medicine.

"If we can better understand Zika virus vertical transmission and successfully block infection in maternal (decidual) cells early in the pregnancy, the virus will not pass through the placenta to reach the fetus and it is less likely to cause severe abnormalities," said Guzeloglu-Kayisli, the paper's lead author.

The widespread global alarm caused by the spread of mosquito-borne Zika virus throughout the Americas in 2015-2016 dissipated after the virus all but disappeared in 2017. Yet, resurgence remains possible in areas where the Aedes aegypti mosquito is prevalent, and there is no

treatment or vaccine available for Zika virus infection.

While most Zika-infected adults show no symptoms, the virus can cause minor flu-like symptoms, and in rare cases has been associated with Guillain-Barre syndrome. However, Zika poses the most concern for pregnant women, because up to one in 10 newborns of affected mothers suffer Zika-associated birth defects, including smaller than normal head size (microcephaly) that can lead to developmental disabilities and other health problems. Zika has also been linked to pregnancy complications, including preterm birth, preeclampsia and miscarriage. Moreover, timing appears important. Mothers infected in the first trimester are much more likely to have babies with severe Zika birth defects than mothers infected in the third semester.

The placenta, the organ supplying maternal oxygen and nutrients to the growing fetus, has ways to prevent most pathogens, including viruses, from crossing its protective maternal-fetal barrier. A subtype of fetally-derived placental cells known as syncytiotrophoblasts, in direct contact with maternal blood, are assumed to be the site where the Zika virus enters the placenta, leading to potential fetal infection. However, Dr. Ozlem Guzeloglu-Kayisli said, these particular trophoblasts resist Zika virus attachment and replication.

To learn more about how Zika gets through the placental wall, the USF Health team began by investigating the cellular and molecular mediators of Zika virus replication. Among their key findings, the researchers:

- Showed that specialized uterine cells from both pregnant and nonpregnant women were highly infectable by Zika virus. These immunologically active decidual cells, which line the uterus in preparation for and during pregnancy, form the maternal part of the placenta closest to the fetus.
- Identified a more than 10,000-fold higher expression of the Zika

virus attachment-entry receptor in the maternal decidual cells than in the fetal trophoblasts. Once inside the maternal cells, the Zika virus (an RNA virus) hijacks the cellular machinery to make proteins needed to copy its genetic material and churn out new viral particles. The proliferation of viral particles released from the maternal cells are then transmitted through branch-like vascular projections (villi) on the placenta's surface layer where they can infect fetal trophoblast cells otherwise resistant to Zika virus.

- Found that the efficiency of viral replication was significantly greater in first-trimester decidual cells than in those from term pregnancies.
- Concluded that maternal (decidual) cells likely serve as the source for initial Zika virus infection and enhance subsequent transmission through the placenta to the fetus. "Moreover, trimester-dependent responses of decidual cells to Zika virus help to explain why pregnant women are susceptible to Zika infection and why the subsequent effects are more detrimental in the first trimester than in late pregnancy," the study authors wrote.
- Demonstrated that tizoxanide, the active metabolite of FDA-approved antiparasitic drug nitazoxanide, effectively impeded Zika virus infection in both maternal decidual cells and fetal trophoblast cells. The drug has been shown preclinically to inhibit a broad range of flu-like viruses and is being tested clinically against coronavirus. The finding warrants further testing of tizoxanide to block perinatal transmission of Zika virus and thereby protect the fetus from harmful outcomes, the researchers conclude.

More information: Ozlem Guzeloglu-Kayisli et al, Zika Virus–Infected Decidual Cells Elicit a Gestational Age–Dependent Innate Immune Response and Exaggerate Trophoblast Zika

Permissiveness: Implication for Vertical Transmission, *The Journal of Immunology* (2020). DOI: 10.4049/jimmunol.2000713