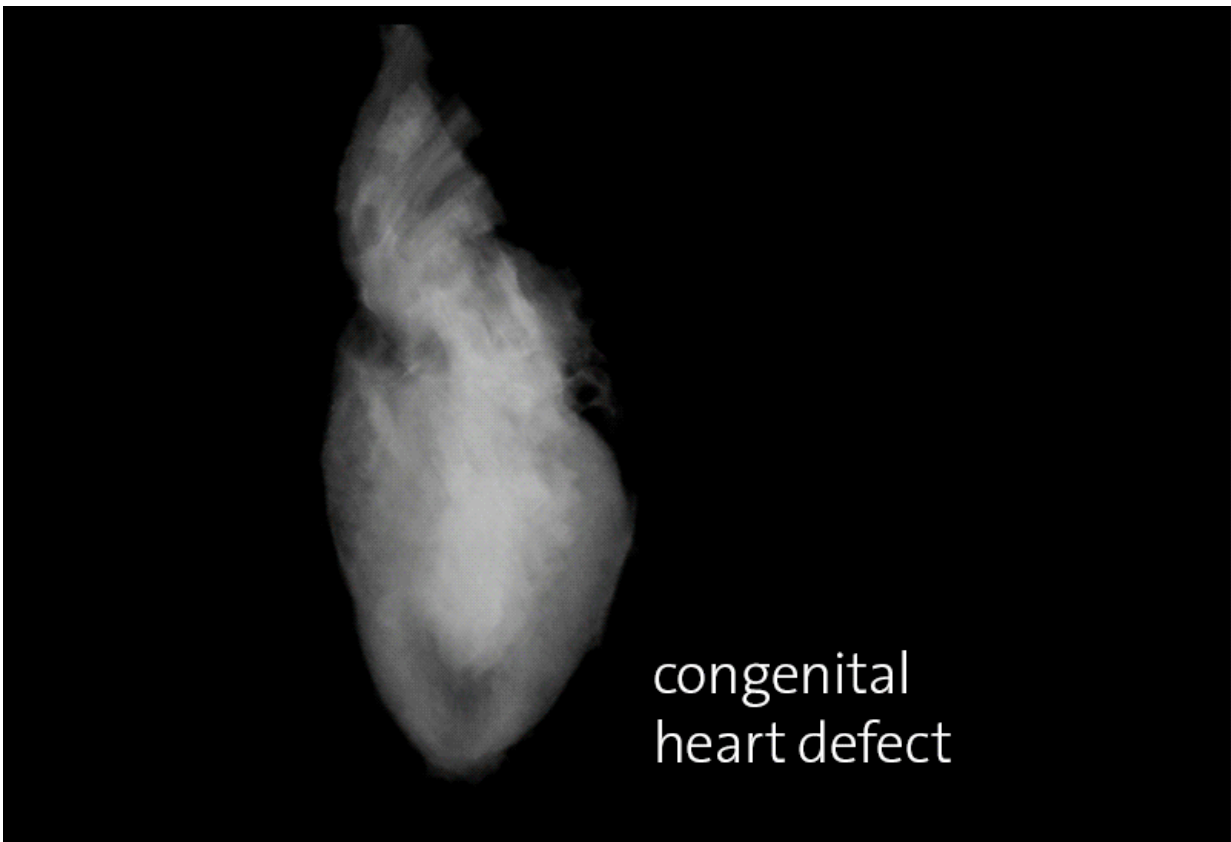


How fever in early pregnancy causes heart, facial birth defects

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Congenital heart defect in chicken. Samiha Khanna

Researchers have known for decades that fevers in the first trimester of pregnancy increase risk for some heart defects and facial deformities such as cleft lip or palate. Exactly how this happens is unclear. Scientists

have debated whether a virus or other infection source causes the defects, or if fever alone is the underlying problem.

Duke researchers now have evidence indicating that the fever itself, not its root source, is what interferes with the development of the heart and jaw during the first three to eight weeks of pregnancy. Their findings, demonstrated in animal embryos, will be published Oct. 10 in the journal *Science Signaling*.

The results suggest a portion of [congenital birth defects](#) could be prevented by lowering the mother's fever with the judicious use of acetaminophen during the first trimester, said senior author Eric Benner, M.D., Ph.D., a neonatologist and assistant professor of pediatrics at Duke.

"My hope is that right now, as women are planning to become pregnant and their doctors advise them to start taking prenatal vitamins and folic acid, their doctor also informs them if they get a fever, they should not hesitate to call and consider taking a fever reducer, specifically acetaminophen (Tylenol), which has been studied extensively and determined to be safe during the first trimester," Benner said. "While doctors advise most women to avoid any drug during pregnancy, there may be benefits to taking acetaminophen to reduce fever. Women should discuss all risks and benefits with their doctors."

Benner cautions that nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and aspirin also reduce fevers, but some NSAIDs are not safe to use during the later stages of pregnancy. There is also ongoing debate over whether sustained use of acetaminophen is safe during pregnancy to manage ongoing conditions such as arthritis, Benner said.

"However, its judicious use for an acute problem such as fever is considered safe. These findings suggest we can reduce the risk of birth

defects that otherwise could lead to serious health complications requiring surgery," he said.

To observe how fever impacts a developing fetus, the researchers studied zebrafish and chicken embryos. Among their discoveries, the scientists found that neural crest cells—cells that are critical building blocks for the heart, face and jaw—contain temperature-sensitive properties.

"We found that these neural crest cells contain temperature-sensitive ion channels that typically are found in your sensory neurons," Benner said. "They're the channels that, when you stick your hand in a hot cup of water, tell your body the temperature has changed."

The Duke researchers engineered a noninvasive magnet-based technology to create fever-like conditions in two specific temperature-sensitive ion channels called TRPV1 and TRPV4 in the neural crest cells involved in developing the heart and face. When those [neural crest cells](#) were subjected to conditions mimicking a transient fever, the embryos developed craniofacial irregularities and [heart defects](#), including double outlet right ventricle, Tetralogy of Fallot and other outflow obstructions.

The type of [defect](#) depends on whether the fever occurs during heart development or head and face development. What researchers still do not know is whether or how the severity or duration of a fever impacts development, Benner said.

"We have known since the early 1980s that fevers are associated with birth defects, but how that was happening has been a complete mystery," Benner said. It is challenging to gather data from mothers on the circumstances, severity or duration of a fever from many months before, he said.

"I hope moving forward, we can educate more women about fever as a

risk factor for [birth defects](#) and let them know they shouldn't just tough it out if they develop a fever," Benner said. "They should ask their doctor before getting pregnant whether they may benefit from taking a fever-reducer such as acetaminophen in the event they develop a [fever](#)."

More information: "Temperature-activated ion channels in neural crest cells confer maternal fever-associated birth defects," *Science Signaling* (2017). [stke.sciencemag.org/lookup/doi ... 26/scisignal.aal4055](https://www.sciencemag.org/lookup/doi/10.1126/scisignal.aal4055)

Provided by Duke University Medical Center

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