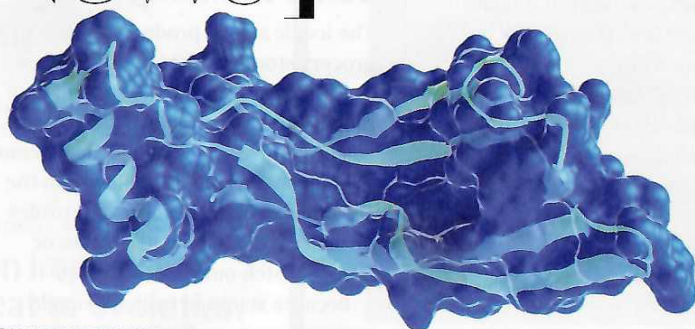


News

Fetuses release large amounts of a hormone called GDF15 (illustrated), which can cause pregnant people to vomit.



HEALTH & MEDICINE

A fetal protein causes morning sickness

Sensitivity to the hormone GDF15 ups the risk for severe illness

BY TINA HESMAN SAEY

A surge of a hormone made by fetuses triggers the stomach-turning nausea and vomiting of morning sickness, a new study suggests.

People who have naturally low levels of the hormone in their blood before pregnancy are more susceptible to a severe form of morning sickness called hyperemesis gravidarum when hit with the rush of hormone, researchers report December 13 in *Nature*. The findings could help identify people at risk of the severe illness and lead to treatments.

Up to 80 percent of pregnant people get nauseous in the early stages of pregnancy, and about half vomit—a combo of symptoms often called (misleadingly) morning sickness. A small percentage of pregnant people—up to 3 percent—will develop hyperemesis gravidarum, vomiting so severe and frequent it can lead to weight loss, dehydration and even hospitalization and death of the fetus or mother.

Previously, researchers speculated morning sickness is caused by estrogen or other hormones that are elevated early in pregnancy, says gynecologist and obstetrician Jone Trovik, who was not involved in the study. For severe sickness, studies implicated elevated thyroid hormone, infections and other causes.

“Most problematic has been that it has been considered to be a psychological cause, which has been widely refuted,”

says Trovik, of Haukeland University Hospital and the University of Bergen in Norway. “Women have been told, ‘Maybe you don’t want this pregnancy. Maybe you’re angry with your husband.’”

The new findings, Trovik says, provide “evidence that this is a real disease.”

Patients who had nausea and vomiting during pregnancy had higher levels of a hormone called GDF15 in their blood than pregnant people without the symptoms, endocrinologist Stephen O’Rahilly of the University of Cambridge and colleagues report. That hormone, which is made throughout the body and helps cells respond to stress, was previously found to act on a part of the brain involved in producing nausea and vomiting.

Study coauthor Marlena Fejzo and colleagues had already shown that people with a certain genetic variant in the GDF15 gene have up to 10 times the risk of developing hyperemesis gravidarum as people without the variant. But those with the variant produce less GDF15 than is typical, those researchers discovered.

That finding was a conundrum, says Fejzo, a geneticist at the Keck School of Medicine of the University of Southern California in Los Angeles. If people with the variant produce low levels of GDF15, but high levels are associated with nausea and vomiting, why is the variant a risk for severe morning sickness?

Turns out that people with the variant

make less GDF15 before pregnancy have elevated levels in their blood when pregnant. The twist is that most of GDF15 produced in pregnancy comes from the fetus and placenta, the new study shows. People with the variant aren’t used to GDF15’s sick-making effects. “So when you’re met with those high levels in early pregnancy, you’re highly sensitive to them more than the average person,” Fejzo says.

Conversely, people with a rare blood disorder called beta thalassemia have low levels of GDF15. Those people rarely get queasy during pregnancy, the research found, which suggests that exposure to the hormone before pregnancy might desensitize people so they don’t become so sick.

The team tested the idea in mice. Rodents that got a big dose of GDF15 back on eating, as expected for nausea in mice. But if the mice were given a small dose of long-acting GDF15 three days before the surge, they weren’t bothered as much. The result suggests that small amounts of the hormone can blunt the effect of a bigger dose later.

All the findings together suggest avenues for treatment. The diabetes drug metformin raises GDF15 levels and might be given to people at risk of hyperemesis gravidarum before pregnancy, O’Rahilly says. Or, future drugs may be developed to block the action of GDF15 on the brain.

Most of the genetic studies were done in people of European descent, Fejzo notes, so it’s not certain that GDF15 is a major player for all ethnic groups.

Before any treatment can be given, scientists will need safety data from animal studies, says Sumona Saha, a gastroenterologist at the University of Wisconsin School of Medicine and Public Health in Madison. No one knows what effect blocking GDF15 may have on fetal development or if raising levels of the hormone before pregnancy could affect conception.

Currently, doctors treat people with severe nausea and vomiting with a variety of anti-nausea medications, neurologic drugs, intravenous fluids and other therapies. Those approaches “are like taking a hammer to a problem,” Saha says. With GDF15, “we potentially will have an X-Act knife that we can use.” ■