Medical Xpress

How pregnancy turns the stress response on its head

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The link between psychological stress and physical health problems generally relates to a stress-induced immune response gone wild, with inflammation then causing damage to other systems in the body. It's a

predictable cascade—except in pregnancy, research suggests.

Scientists exploring the negative effects of prenatal stress on offspring mental health set out to find the immune cells and microbes in stressed pregnant mice most likely to trigger inflammation in the fetal brain—the source for anxiety and other psychological problems identified in previous research.

Instead, the researchers found two simultaneous conditions in response to stress that made them realize just how complex the cross-talk between mom and baby is during gestation: Immune cells in the placenta and uterus were not activated, but significant inflammation was detected in the fetal brain.

They also found that prenatal stress in the mice led to reductions in gut microbial strains and functions, especially those linked to inflammation.

"I thought it was going to be a fairly straightforward tale of maternal inflammation, changes in microbes and fetal inflammation. And while the changes in microbes are there, the inflammation part is more complex than I had anticipated," said Tamar Gur, senior author of the study and assistant professor of psychiatry and behavioral health, neuroscience, and obstetrics and gynecology at The Ohio State University.

"The complex interplay between the stress response and the immune system is dysregulated by stress, which is problematic for the developing fetus. There are key changes during this critical window that can help shape the developing brain, so we want to figure out how we could potentially intervene to help regulate these systems."

The study was published recently in *Scientific Reports*.

Most attention paid to the negative effects of prenatal stress on offspring mental health focus on disruptive major life events or exposure to disaster, but evidence also suggests that up to 84% of pregnant women experience some sort of stress.

In a previous study, Gur's lab found that prenatal stress's contributions to life-long anxiety and cognitive problems in mouse offspring could be traced to changes in microbial communities in both mom and baby.

Gur focuses on the intrauterine environment in her search for factors that increase the risk for prenatal stress's damaging effects, and this newer study opened her eyes to how complicated that environment is.

"The dogma would be that we're going to see an influx of immune cells to the placenta. The fact that it's suppressed speaks to the powerful anti-inflammatory response of the mom. And that makes sense—a fetus is basically a foreign object, so in order to maintain pregnancy we need to have some level of immunosuppression," said Gur, also an investigator in Ohio State's Institute for Behavioral Medicine Research and a maternal-fetal psychiatrist at Ohio State Wexner Medical Center.

"We want to figure out what is at the interface between mom and baby that is mediating the immunosuppressive effect on the maternal side and the inflammation on the fetal side. If we can get at that, we'll get really important keys to understanding how best to prevent the negative impact of prenatal stress."

Prevention could come in the form of prebiotics or probiotics designed to boost the presence of beneficial microbes in the GI tract of pregnant women. Maternal microbes affect the brains and immune systems of developing offspring by producing a variety of chemicals the body uses to manage physiological processes.

"I think microbes hold really important clues and keys, making them a tantalizing target for intervention. We can do things about individuals' microbes to benefit both mom and baby," Gur said.

To mimic prenatal stress during the second and early third trimesters, pregnant mice in her lab are subjected to two hours of restraint for seven days to induce stress. Control mice are left undisturbed during gestation.

In this recent study, the researchers found stress in mice activated steroid hormones throughout the body—the sign of a suppressed immune system—and resulted in lower-than-expected populations of immune cells in reproductive tissue, suggesting that the uterus was effectively resisting the effects of the stress.

An examination of colon contents showed differences in microbial communities between stressed and non-stressed mice, with one family of microbes that influences immune function markedly decreased in stressed mice. The researchers found that stress showed few signs of gene-level changes in the colon that could let bacteria escape to the bloodstream—one way that microbes interfere with body processes.

"There are absolutely changes in microbes that might help explain key pathways that are important for health and the immune system, especially when it comes to the placenta and the mom's immune system," Gur said.

In future studies, her lab will examine immune cells in the fetal brain and monitor how gene expression changes in cells in the placenta in response to stress. She is also leading an ongoing observational study in women, tracking microbes, inflammation and stress levels during and after pregnancy.

More information: Adrienne M. Antonson et al. Unique maternal

immune and functional microbial profiles during prenatal stress, *Scientific Reports* (2020). DOI: 10.1038/s41598-020-77265-x