New Study Points to Cause of Fetal Fentanyl Syndrome

Paper published in Molecular Psychiatry *advances work that began at Nemours Children's Health*

A new paper out earlier this spring from a national team of researchers has suggested an explanation for recently discovered Fetal Fentanyl Syndrome.

This newly discovered syndrome, first reported in 2023 by Karen Gripp, MD, a geneticist at Nemours Children's Health and professor of pediatrics at Thomas Jefferson University, and her collaborators, causes distinctive physical birth defects, including cleft palate, distinctive facial features, and unusually small heads. While these physical findings resemble those seen in a metabolic disease of genetic origin, Smith-Lemli-Opitz syndrome (SLOS), these patients did not have a metabolic disease. Rather, this novel syndrome is related to non-prescription fentanyl use by mothers during early and mid-pregnancy. This novel syndrome was termed fetal fentanyl syndrome (FFS).

The syndrome caught the eyes of Karoly Mirnics, MD, PhD, director of the University of Nebraska Medical Center Munroe-Meyer Institute, and Zeljka Korade, DVM, PhD, professor of pediatrics at UNMC, because it closely resembled the features of Smith-Lemli-Opitz syndrome (SLOS), a developmental disability arising from disruption of the body's ability to synthesize cholesterol.

The Korade and Mirnics laboratories, which have been studying the developmental role of cholesterol for about two decades, proposed that the mechanism by which SLOS and FFS arise might be related. Barely six months later, with a new study recently published in *Molecular Psychiatry*, a team led by Drs. Mirnics, Korade, Gripp and Ned Porter, PhD, a research professor in the Vanderbilt Department of Chemistry and Institute of Chemical Biology, may have explained how this novel syndrome arises.

The key? The new study found that the cause of FFS may be fentanyl's disruption of the baby's ability to make cholesterol, related to fentanyl exposure in the womb.

"Cholesterol is essential for development," Dr. Mirnics said. "Without cholesterol, you cannot survive. If you have impaired cholesterol production, the developing brain and body are impacted."

"Fentanyl not only impairs the synthesis of cholesterol, but it also leads to the build-up of the same highly toxic sterols in cells that are found in SLOS patients," Dr. Porter said. "It seems likely that the presence of these toxic compounds during fetal development plays a large part in the syndrome." The Porter Research Group at Vanderbilt has studied these toxic compounds in collaboration with the UNMC researchers for over a decade.

Dr. Gripp said the new work was an important next step following the initial identification of FFS.

"We thought that the fentanyl was the likely reason for this new syndrome," she said. "But we could not prove this beyond reporting what we saw. This second paper is so important, because in an in vitro assay, they show that indeed fentanyl can have effects that would result in the findings we see."

In the recent study, researchers used multiple cell models to test whether fentanyl could be interfering with the body's ability to make cholesterol, potentially leading to FFS. They exposed different types of mouse and human cells to fentanyl. The result: the fentanyl exposure disrupted multiple steps in the cholesterol-making process. But the results also posed another question. Why don't all children of mothers using non-prescription fentanyl end up with FFS?

The researchers found in this study that cells with one mutated copy of the gene that causes Smith-Lemli-Opitz are increasingly susceptible to adverse effects of fentanyl. That leads to about 3% of the population, Dr. Mirnics said.

"Not everyone is equally susceptible," Dr. Mirnics said. "The potentially adverse effects of any medication or chemical compound might depend on your genes, lifestyle and environmental factors. One drug might not cause problems for me and might be catastrophic for you."

"The effects of fentanyl may also be exacerbated by some prescription medications if taken at the same time during a pregnancy," Dr. Porter said. "It's been a surprise to find so many highly prescribed medications that cause the same biochemical effect as does fentanyl. Fentanyl exposure while taking one or more of these prescription medications will likely compound the effect of fentanyl alone."

Dr. Gripp was pleased to work with the UNMC team.

"The Korade lab has been working on the cholesterol metabolism, which is affected in Smith-Lemli-Opitz syndrome, so they had been involved in similar work," Dr. Gripp said, adding that her team had cited work from the Korade and Mirnics labs in the 2023 paper. "They were able to use their experience, their assays and show that fentanyl did indeed have the effect we anticipated, in the sense that it affects cholesterol metabolism."

The researchers stressed that fentanyl is safe when prescribed and used appropriately, and that further validation studies are needed in pregnant mouse models and human patients. These studies are ongoing and are a focus of a new grant

application to the National Institutes of Health.

The new study is a “remarkable” example of addressing a health crisis by combining strong basic science and genetics with a broader understanding of factors that can disrupt the developing brain, said Pat Levitt, PhD, chief scientific officer and vice president and director of the Saban Research Institute, who was not affiliated with the study.

“That they have made the connection between a neurodevelopmental disorder in which cholesterol production is key with that occurring due to prenatal fentanyl exposure, but only in those individuals that have genetic risk, is even more remarkable given the pace at which they made these new discoveries,” Dr. Levitt said.

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