Effects of antidepressants taken during pregnancy are poorly understood, scientists note

December 13 2022, by Mônica Tarantino

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Depression affects 10%-16% of pregnant women worldwide. Most get better with the help of antidepressant drugs.

Although the safety of using antidepressants during pregnancy is endorsed by science, their effects on fetal neurodevelopment are poorly understood and should be studied with advanced techniques such as genomics. This is the main conclusion reached by a group of Brazilian researchers in a review of more than 100 scientific articles on fetal exposure to these drugs, especially sertraline, the most prescribed antidepressant worldwide.

"Most of the publications we reviewed were reports of observational surveys and studies conducted in the laboratory using cell cultures and animals, whose brain development is very different from that of humans. They don't offer sufficient data to justify conclusive results," said neuroscientist Alexandre Kihara, a researcher at the Neurogenetics Laboratory of the Federal University of the ABC (UFABC) in São Bernardo do Campo, São Paulo state.

"We propose an experimental trial model involving human-induced pluripotent stem cells [hiPSC] to investigate what happens to developing fetal nerve cells in pregnant women during treatment with antidepressants," said Luciana Rafagnin Marinho, a researcher at UFABC with doctoral and postdoctoral qualifications in epigenetics, in vitro embryo production and animal reproduction.

Marinho and Kihara are first and last authors respectively of the review article published online in *Seminars in Cell & Developmental Biology* and soon to be available in print.

Human induced pluripotential stem cells can be differentiated into brain organoids ("mini-brains"), which scientists want to use in research on neurodegenerative diseases such as Parkinson's and Alzheimer's, and in testing of drugs with neurological action.

"These structures can be used to test different dosages and track the

development of brain cells up to the third trimester," said Alysson Muotri, penultimate author of the article. Muotri is a neuroscientist at the University of California San Diego (UCSD) in the United States and heads a genetics laboratory that has pioneered the development of brain organoids to study autism and other neurological disorders. He is also a co-founder of Tismoo, a Brazilian biotech startup.

"We can study the organoids for up to a year, observing aspects of their development such as the morphology and electrophysiology of individual neurons or neural networks," he explained.

To exemplify the possible advances, Marinho cited the only study that used brain organoids among the more than 100 covered by the review. "It investigated the effects of paroxetine and detected a reduction in the growth of neurites [projections from neurons that develop into axons and dendrites to form complex circuits] and the population of oligodendrocytes, which produce the myelin sheath around axons and are therefore important to enable information to travel through the nervous system," she said.

The scientists note that whole-genome sequencing, transcriptome analysis and single-cell RNA sequencing apply to research using organoids. "The technology enables us to investigate the effects of exposure to antidepressants on different cell types, such as progenitor cells, glial cells and neurons. This is particularly important because alterations may not be confined to neurons. We need to know all these implications," Kihara said.

Caution is required in interpreting the findings of this kind of research. "We're not saying antidepressants shouldn't be used in pregnancy. We're proposing an experimental model and stressing the need to study their effects on neurodevelopment with the most advanced resources available so that potential alterations can be managed," Kihara said.

More information: Luciana Simões Rafagnin Marinho et al, The impact of antidepressants on human neurodevelopment: Brain organoids as experimental tools, *Seminars in Cell & Developmental Biology* (2022). DOI: 10.1016/j.semcdb.2022.09.007

Provided by FAPESP