

Studies explore links between stress, choline deficiency, preterm births, and mental health

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In two recent articles published in *Schizophrenia Bulletin*, Sharon Hunter, Ph.D., an associate professor in the University of Colorado School of Medicine Department of Psychiatry, and M. Camille Hoffman, MD, MSc, an associate professor in the University of Colorado School of Medicine Department of Obstetrics and Gynecology, along with their research group, have uncovered a potential link between choline deficiency in Black pregnant women in the United States and increased risk of developmental and behavioral issues that can evolve into mental illness later in their children's lives.

The first article, published in November 2020, is a study, titled, "Black American Maternal Prenatal Choline, Offspring Gestational Age at Birth, and Developmental Predisposition to Mental Illness." The second, published last month and titled "Targeting Treatments to Health Disparities," is a follow-up article delving more deeply into known healthcare disparities highlighted by the study results.

The studies are the result of more than 20 years of research by the group, which began with a general goal of understanding in utero risk factors of schizophrenia.

"At that time, there was a lot of discussion around the idea that mental illnesses like schizophrenia were tied to prenatal neurodevelopment," Hunter says.

Early choline clinical trial

Choline is an essential nutrient that can be found in foods such as milk, red meats, and eggs. Based on previous studies of choline showing that it is vital for fetal neurodevelopment, including the development of inhibitory neurocircuits in the brain that are abnormal in individuals with schizophrenia and many of their family members, the group launched its first clinical trial in 2004. During the trial, they supplemented pregnant women with a specific form of choline called phosphatidylcholine, then monitored their children until the age of four. Phosphatidylcholine is less likely to cause side effects, such as stomach upset, associated with pure choline. The results of the trial showed that those inhibitory neurocircuits were functioning properly in more children from supplemented moms than in children whose mothers didn't receive the supplement.

"It showed that mothers who had lower choline levels during the second trimester of pregnancy gave birth to babies who were more likely to have worse neurodevelopmental scores, which can be a marker for later mental illness or behavioral problems," Hoffman says.

The ultimate goal was to uncover whether supplementing with choline could help prevent schizophrenia, but since the condition isn't typically

diagnosed until a patient is in their 20s, the group instead monitored for the some of the disease's early indicators.

"We couldn't follow these children for 20 years, but we could test them as children to see if they had problems with attention or withdrawal or aggression, which can be indicators not just of schizophrenia but of other mental issues as well," Hunter explains.

Uncovering a racial health care disparity

After the first choline trial, the group conducted a follow-up study in which they measured choline levels in 183 pregnant women. Although the women were told about choline and the researchers suggested that they try to get more choline in their diets, they did not administer any choline supplements to the participants. It was during this study that the group noticed a demographic disparity: overall, choline levels were markedly lower in Black women than any other group.

"When we found these differences in choline levels, we started to wonder whether this also translated to differences in outcomes," Hunter says. "And preliminary data suggests that it does."

This disparity in choline levels prompted the researchers to look back at the results of the first clinical trial. When they did, they found that the gestational age at delivery in Black mothers who had been supplemented with choline was extended by an average of three weeks compared to Black mothers who didn't receive supplementation.

"As an Ob/Gyn, [preterm birth](#) is one of the main adverse pregnancy outcomes that we're always working towards preventing," Hoffman says. "And there are known disparities in both birth weight and risk of preterm birth between Black women and their children and almost every other group."

Since preterm birth can have adverse effects on the development of cognition and behavior throughout childhood—including mental health—the results of the clinical trial and the subsequent observational study seem to point to two potential benefits of choline

supplementation for pregnant women, and, in particular, Black women: enhanced prenatal development of inhibitory neuro-circuits in the brain and older gestational age at delivery.

How systemic racism in the U.S. may play a role in stress and pregnancy

Now the researchers were faced with the question of why Black mothers' choline levels were so much lower than those of other women? They compared the choline levels of the Black pregnant women in the American study to blood samples from a cohort of pregnant women in Uganda and found that the choline levels of the Ugandan women were much higher than their American counterparts.

"Of course, we know that not all Black women in America are African American or of African heritage, Hunter says. "But still, it seemed like there was something else going on that might account for the racial differences we were seeing."

So, they turned their attention to a potential culprit and differentiator: stress.

"Part of my contribution to the research group early on was looking at ways to capture and measure stress in relation to two primary pregnancy outcomes," Hoffman says. "One was gestational age at birth and the other was birth weight, because both of those are markers for either long-term wellness or potential impairments."

One of the group's hypotheses was that the more stressed a mother is, the more her liver may sequester choline for itself, meaning that the fetus may not receive an adequate amount for neurodevelopment and is more at risk for preterm birth.

The team used Hoffman's methods to collect measures of maternal stress in the observational study participants. And while the Black women didn't report feeling more stress, their hair cortisol levels, a biomarker of stress exposure, were higher than those of participants of other races.

"Even though they don't report it, their bodies looked more stressed," Hunter says. "Our question

now is whether there are stressors that Black women experience but that our questionnaires do not capture, or are cortisol levels reflecting accumulated exposure to low-level, background stressors, perhaps stemming from decades or lifetimes or even generations of institutional racism in this country. We don't have the data to answer those questions yet, but we wanted to get this study out there to say, 'this is something we should be paying attention to.'"

Could choline be the next folic acid?

The Food and Drug Administration (FDA) currently recommends that pregnant women get 550 milligrams of choline a day, but Hunter says that about 90% of pregnant women don't meet that goal.

"That's hard to do," she says. "It's not that it can't be done, but it would be difficult. There have also studies that tried to raise choline levels in women by bringing them into a laboratory and providing them with high-choline foods, but they were not very successful."

"The same was true for folic acid studies 20 years ago," says Hoffman. "We recommend folic acid for [pregnant women](#) because it has a major impact on reducing neural tube defects. But the same story played out back in the early days of folic acid research, where the risk was significantly reduced when folate was included in a supplement versus trying to get people achieve adequate dietary intake. Dietary changes are hard to make, but we know you're going to get higher choline levels when you supplement."

Hunter says the group hopes to do another clinical trial in the future where they supplement one cohort of Black women at the FDA-recommended choline level, plus another group at about two to three times the recommended amount to see if there is any additional benefit to supplementing at a higher level.

"If we're telling women that they need 550 milligrams of choline per day, but some other factor limits how much choline can get to the fetus, that level of intake may not adequately meet the needs of the developing fetus. We need to understand

this," she says.

Unfortunately, the supplements can be expensive: usually \$600-\$800 over the course of a pregnancy, and up to about \$1,200 for some of the more expensive supplements.

Both Hoffman and Hunter hope to continue to raise awareness around this issue and the health disparity when it comes to Black women.

"For over 50 years, maternal fetal medicine has been trying to figure out ways that we can reduce preterm birth, and then we find a promising contender in the choline data set," Hoffman says. "It's especially exciting because a major push in obstetrics right now is trying to close these known gaps in outcomes that exist for Black [women](#) and their children. The [choline](#) and cortisol connection gives us objective, physiologic measures to sort out what changes we need to make in terms of addressing [health disparities](#)"

More information: Sharon K Hunter et al, Targeting Treatments to Health Disparities, *Schizophrenia Bulletin* (2021). DOI: [10.1093/schbul/sbab051](https://doi.org/10.1093/schbul/sbab051)

Sharon K Hunter et al, Black American Maternal Prenatal Choline, Offspring Gestational Age at Birth, and Developmental Predisposition to Mental Illness, *Schizophrenia Bulletin* (2020). DOI: [10.1093/schbul/sbaa171](https://doi.org/10.1093/schbul/sbaa171)

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