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Acetaminophen Use in Pregnancy—Study Author Explains the Data

Kate Schweitzer

A study published in *JAMA* last year has come into the spotlight in recent days following a controversial warning about the use of a common pain reliever. The research studied acetaminophen (paracetamol) use during pregnancy and its possible connection to children's risk of autism and other neurodevelopmental disorders. The heightened interest in the study follows warnings by the US Food and Drug Administration (FDA) and President Donald Trump that have startled the medical community and left pregnant people across the nation confused.

On September 22, the FDA issued an alert to physicians nationwide that the use of acetaminophen by pregnant women may be linked to an increased risk of neurological conditions, such as autism and attention-deficit/hyperactivity disorder (ADHD), in their children. The agency also initiated the process for a label change to products containing acetaminophen, most notably Tylenol, which remains the only over-the-counter medication approved for treating fever in pregnancy.

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The FDA cited 2 cohort studies in a press release explaining its change in guidance but acknowledged that a "causal relationship has not been established." Despite this, it suggested that clinicians should consider recommending that their patients minimize the use of the drug for routine, low-grade fever.

The same day, during a press conference, Trump urged pregnant women not to take Tylenol and encouraged them to "tough it out."

Following these developments, the World Health Organization issued a statement emphasizing that, although extensive research—including large-scale studies—looking into links between acetaminophen use during pregnancy and autism has been undertaken during the past decade, no consistent association has been found.

The study published in *JAMA* in April 2024 is among the most recent to investigate this question. In it, researchers followed up 2.5 million children born in Sweden between 1995 and 2019 for more than 2 decades. Using sibling controls to account for genetic and other environmental cofounding factors, they found no increased risk in autism, ADHD, or intellectual disabilities in the children of women who used acetaminophen during pregnancy.

To provide clarity on this issue, *JAMA* Deputy Editor Linda Brubaker, MD, MS, an obstetrician-gynecologist, spoke with the study's senior author, Brian Lee, PhD, a professor of epidemiology at Drexel University Dornsife School of Public Health. They discussed the study's methods and findings, the importance of scientific rigor in investigating these questions, and the potential effects on patient care that come with discouraging acetaminophen use during pregnancy.

This interview has been edited for clarity and length.

JAMA: General clinical guidance has always been to use medication cautiously during pregnancy for effective treatment of fever or pain, both of which are clear indications for the use of acetaminophen during pregnancy. Yet there have been conflicting reports on whether acetaminophen used during pregnancy increases the risk of neurodevelopmental disorders. I'd like you to describe the major findings of the study you and your coinvestigators published in *JAMA*.

DR LEE: Our study conducted in Sweden looked at 2.5 million pregnancies. The mothers and their children were followed for over 20 years, and we were able to do this using the national computerized register system. What we found—it's actually a 2-part story. The first part is that when we looked at the children born to mothers who used acetaminophen during pregnancy and compared them to the children born to mothers who didn't use acetaminophen, we saw an apparent statistical association between acetaminophen use and risk of autism, ADHD, and intellectual disability. But association is not causation.

And so, the second part of our story is that we wanted to test out if this association was causal. Now, the children born to mothers who use acetaminophen, these mothers are different in many ways from mothers who don't use acetaminophen. As you mentioned, there are indications for use—headaches, infections, fevers—things that have been plausibly associated with autism and other conditions in the past. And these are what we call confounders, a third factor that might explain an association.

One of the examples I use in the classroom to explain confounding is eating ice cream and risk of drowning. And the idea here is that ice cream is statistically associated with risk of drowning, but this is not a causal association. It is actually hot weather that increases ice cream consumption as well as increases likelihood of swimming, which would increase likelihood of drowning.

So, we wanted to test whether this statistical association was real or not, and the way we did this was that we did a sibling control analysis. Basically, we can compare, within the same parents, siblings where one was exposed to acetaminophen in the womb and one was not. There's a couple of different reasons for doing this, but one of the biggest elephants in the room when it comes to confounding is genetics. For neurodevelopmental disorders especially, they are highly heritable, and genetics comprises a substantial proportion of their cause. So studies that don't take into account genetics may come to different conclusions than studies that do take into account genetics. When we do the sibling control analyses, all of the statistical associations completely disappeared. In other words, the associations did not appear to be causal.

JAMA: You went out of your way to design a study that was very, very rigorous, and we typically think of randomized controlled trials as generating the highest level of evidence. That's not really possible or feasible for this research question. What did you and your coauthors do to make the study design as rigorous as possible?

DR LEE: It is difficult to conduct an ethical, randomized controlled trial of pregnant women, and—especially for these neurodevelopmental disorders—follow them up for many, many years.

So, first of all, thanks to the health register system, we had comprehensive medical history on the mothers and the fathers as well as the kids themselves. And this is extremely important because, as I mentioned before, the indications for acetaminophen use could confound. So we have data on things like infections and rheumatoid arthritis, which might increase pain.

We have cutting-edge statistical methods where we are able to control for these sorts of confounders. Our exposure assessment is always something to ask about because, how do you ascertain a mother's acetaminophen use during pregnancy? Studies that look at this retrospectively are going to have a challenge because if you ask someone, "Oh, what did you take for pain 10 years ago?" it's going to be very difficult. Our study had the advantage of being prospectively collected. In other words, these data on acetaminophen use were collected at the time of pregnancy, so it was less likely to have recall issues.

JAMA: Not only did you collect prospective exposure, you were also able to get some information about dose-responsiveness.

DR LEE: Yes. Acetaminophen is a medication that can be offered over the counter as well as through prescription. What we did have available to us was all prescription drug records at a certain point in time. We were able to, for a subsample of the analysis, look at dose-response. And this is a very clarifying analysis because dose-response is traditionally used as a marker of causality. If something causes an outcome, in theory, more of that exposure should cause more of that outcome. And so, we were able to test this out in our analysis as well.

JAMA: Other studies have found associations between acetaminophen during pregnancy and autism. Why might the results from this study differ from those other studies that report association?

DR LEE: That's an excellent question. There have been, according to a recent review, 46 different studies that have examined acetaminophen use during pregnancy and neurodevelopmental outcomes. There may be more out there, but the evidence is inconsistent. Studies have shown associations with outcomes like ADHD and autism. Other studies have not. The trend that seems to emerge is that the studies that have better control of potential confounders, especially those that do sibling analyses, tend to find no evidence to support a causal association.

JAMA: How will the evidence from this study help patients and their clinicians consider the risks of judicious acetaminophen use in pregnancy?

DR LEE: The traditional way to think about medication use is lowest dose possible for the shortest duration possible, and I don't think this study changes any of that, and certainly not any of the messaging from the administration. What our study does add is evidence to alleviate a mother's concern that taking this medication might be somehow harmful. We had such a comprehensive dataset and such a large sample that inconsistencies due to small sample size variation or inability to control for potential biases—we were able to [avoid] a lot of this. Now, I'm not going to claim that our study is perfect, but it certainly adds a strong measure of evidence to allay any potential concerns.

JAMA: You and your coauthors outlined several limitations to this study. Could you summarize those?

DR LEE: The first and foremost thing is that this is not a randomized controlled trial. That's usually our gold standard of evidence. Because we don't meet that high bar, there's potentially more issues, but, of course, the same can be said for every single study on this topic because there are no randomized controlled trials on this topic. And so, that's one major limitation.

The second is that with any observational study, you run the risk of apples-to-oranges comparisons—namely, the people who are exposed are apples and the people who are unexposed are oranges, and you're comparing these 2 completely different fruits. The way that we did address that issue was to do the sibling controls to get more of that apples-to-apples comparison. But it's of course not going to be perfect like a randomized controlled trial might be.

One of the limitations that we also address is that acetaminophen use in Sweden is lower during our study period than other places around the world. So some critiques of our work have indicated that "70% of pregnant women use acetaminophen during pregnancy." And while that figure might be true for certain samples, there seems to be a tremendous amount of variation depending on which study sample or which time period.

In general, the opponents of our work have mentioned that "the use of acetaminophen was so low in the study that this could not be valid." Use in our population was 7.5% on average over the study period. In contrast, for example, a US study showed 50% to 70%, another US study showed 14%, and a Danish study showed about 6%. These are just numbers that don't necessarily have a lot of relevance for folks, but I'd like to point out that when we did our study the traditional way—which is, you adjust for all the covariates that you have in your data—we did find that statistical association. It was not like our study was biased to begin with, to find no association.

JAMA: [Based on] the cumulative evidence with the contribution of this analysis, where is the science on this topic now?

DR LEE: There is a consistent body of evidence now that is pointing toward no strong effect of acetaminophen on neurodevelopmental outcomes. Just in the last 3 weeks, in fact, our study was replicated in an entirely different population. A nationwide Japanese study with about 200 000 persons looked at this exact same question and also did a sibling analysis. The use of acetaminophen in this population was roughly 40%. And they found the exact same thing that our Swedish study did, where there's an apparent statistical association initially, but it completely disappears when you do the sibling control analysis. And so, the evidence is pointing a certain way that is going to be challenging for other studies to try and overcome.

JAMA: The standard clinical practice for obstetric caregivers is to evaluate and treat fever, especially during the first trimester, knowing the harms that are potentially associated with first-trimester fever. I do think there could be potential harms from avoiding needed acetaminophen use. How can you help patients understand the conflicting messages that are currently in the news in terms of what their clinician is advising and the best standard care for them?

DR LEE: You raise an excellent point. The conflicting messaging is going to be challenging to deal with, and I think it's fortunate that we have expert clinician bodies that have weighed in on this topic. For example, the Society for Maternal-Fetal Medicine and the American College of Obstetricians and Gynecology come to the same conclusion that there's no strong evidence to support that this is a causal association. So, I think where this leaves us is, as before, any pregnant person who has questions about their health should be talking to their physician, and hopefully, the physician will be able to cut through any confusion. ■

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