

NEWS

Autism risk climbs with number of fevers during pregnancy

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Having fevers while pregnant boosts the risk of having a child with autism, according to a study of more than 95,000 women¹.

The link is strongest in the second trimester, when a single fever is associated with a 40 percent increase in autism risk. Three or more fevers after the first trimester triples the risk of having a child with autism, according to the study, which appeared 13 June in *Molecular Psychiatry*.

The findings support the idea that a pregnant woman's immune response, which often includes fever, can disrupt brain development in the fetus, says lead researcher **Mady Hornig**, associate professor epidemiology at the Columbia University.

The study is inconclusive on whether drugs that lower fever mitigate the risk, but the results hint that they might, says **Sarkis Mazmanian**, professor of biology at the California Institute of Technology. Mazmanian was not involved with the study but studies maternal infection as a risk factor for autism. "I'm being very optimistic here, but I think there's value in more research in this space," he says.

In other studies, researchers asked mothers of children with autism to recall whether they had a fever when they were pregnant. In the new work, women answered questions about fevers every four weeks throughout pregnancy. Remembering a fever years after it occurred is difficult, and mothers who have children with autism may be more inclined to incorrectly recall having a fever. So the new study's approach may result in more accurate reports than from previous work.

"This is a major strength, since the questions were asked at a time relatively close to the fever episodes and long before the mothers knew their child's neurodevelopmental status," says **Irva Hertz-Picciotto**, professor of epidemiology at the University of California, Davis, who was not involved in the work.

Tracking temperatures:

Hornig and her team analyzed data from 95,754 **mother-child pairs in Norway**. Of these, 15,701 of the mothers reported on a health questionnaire that they'd had one or more fevers while pregnant. The team followed all of the participants' children until they reached age 9, on average, and found that 583 received an autism diagnosis.

The timing of the fever matters for autism risk, the researchers found. Compared with the 40 percent increase in the second trimester, having a fever in the first trimester carries a 34 percent increase in the risk of autism, but that result is not statistically significant. Having a fever in the third semester has no effect on autism risk.

The researchers also found a dose-response relationship for fever: The increase in risk ranges from 30 percent throughout pregnancy for one or two episodes of fever, to more than threefold for three or more episodes in the second trimester and beyond.

Still, the vast majority of women who have a fever during pregnancy do not have a child with autism and the absolute increase in risk is small. Even among mothers who had three or more fevers, only 5 out of 308 children (about 1.6 percent) have autism, compared with 376 of 65,502 children (about 0.6 percent) whose mothers reported no fevers.

Immune effect:

Another study from the same group, published last week in *mSphere*, found that women with laboratory-confirmed influenza during pregnancy are no more likely than those without the infection to have a child with autism². But women who actually had flu-like symptoms, such as fever, nearly double their risk of having a child with autism, supporting the general idea that inflammatory processes drive the risk, Hornig says. The increase is not statistically significant, but should not be ignored, the team says.

“Although chance may explain our findings, the magnitude of the potential association may be of biological importance,” the researchers write in the paper.

Fever increases the production of white blood cells, which release certain molecules, called cytokines, to fight infections. Mouse studies suggest these molecules can pass into the bloodstream of the fetus through the placenta, and ultimately alter the **expression of genes associated with autism** in the developing brain.

Persistent fevers may cause cytokines to build up, compounding the risk of autism, Hornig says.

“A transient fever that comes and goes quickly perhaps doesn't have as much risk as something that is happening frequently and causing these molecules to increase or perhaps accumulate over

many weeks,” she says.

The effects of fever also may depend on the genetic makeup of the mother, Hornig says. “Some women have an immune response that fails to come back down again after it's done its work,” she says. “There may be genetic factors on the fetus side as well.”

Hornig’s team examined whether medications that lower body temperature would reduce the risk. More than 5,600 women took acetaminophen for fever during their second trimester. The team found an association between acetaminophen use and a decrease in autism risk, but it was not statistically significant. Only 161 women took ibuprofen during the second trimester, and none of them have a child with autism. (About half of pregnant women use acetaminophen at least once, but doctors generally advise against ibuprofen use during pregnancy.)

“Because the numbers were small, we need huge caution,” in interpreting the finding about ibuprofen, Hornig says. But she says the link deserves further investigation.

A 2013 study led by Hertz-Picciotto found that drugs that lower fever mitigate the increase in autism risk associated with fever³.

Hornig plans to explore whether some women are particularly likely to benefit from taking these drugs during pregnancy. “We want to look at the genetic component, to help us provide precision medicine for management of a common phenomenon during pregnancy,” she says. She also plans to measure blood levels of cytokines in pregnant women to understand the molecules’ role in the process.

REFERENCES:

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